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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JANUARY, 1946

ORIGINAL ARTICLES

PREFRONTAL LOBOTOMY

SURVEY OF 331 CASES

BY WALTER FREEMAN, M.D., PH.D., F.A.C.P.

AND

JAMES W. WATTS, M.D., F.A.C.S.

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(From the Department of Neurology, George Washington University)

PREFRONTAL lobotomy represents in some respects the most drastic treatment yet devised for the handling of intractable psychoses and neuroses. Whereas shock methods with insulin, metrazol and electroshock have been shown to produce certain damaging effects upon the brain, they can scarcely be compared, pathologically, with the lesions produced by severing the connections between the thalamus and the frontal lobes of the brain. By the same token, however, prefrontal lobotomy produces therapeutic results in cases that have been unsuccessfully treated by long series of shocks. We believe that there is something specific in the attack upon this region of the brain, something that is not achieved by the general disruption of cortical processes that is accomplished by shock therapies. The comparison has been suggested of the rifle bullet as compared with the shotgun charge.

The surgical treatment of mental disorders was initiated a decade ago by Egas Moniz,[3] following the demonstration in man and in animals that a considerable portion of the frontal lobes could be removed without danger to life, and with preservation of most of the intellectual functions.[2,12]

Egas Moniz reasoned that the stereotyped behavior patterns observed in the course of certain "functional" mental disorders could be occasioned by pathologic stabilization of synaptic connections of cortical cell groups. "In accordance with the theory which we have just developed," he writes, "one conclusion is derived; to cure these patients we must destroy the more or less fixed arrangements of cellular connections that exist in the brain, and particularly those which are related to the frontal lobes." Egas Moniz reported 7 recovered and 7 improved among his first 20 patients.

Early in our work we were impressed with the subtle change that took place in patients thus operated upon. Disproving Egas Moniz' ideas, at least in part, these patients continued to manifest their same hallucinations and delusions, but were no longer bothered by them. It was the emotional reaction to the ideas that had been suppressed. When this fact was more fully investigated it was realized that the incisions in the frontal lobes interrupted the anterior thalamic radiation as described by Herrick,[11] and actually produced degeneration in the nucleus medialis dorsalis of the thalamus as found by

Walker[18] in lobectomized monkeys. This radiation is clearly seen in some of Flechsig's[5] charts, having become myelinated long before the association pathways in the same area.

Clinical studies on patients with lesions of the frontal lobes, and investigations upon animals whose frontal lobes had been removed[2,4,10,12,13,14] dealt largely with intellectual functions. The results were far from uniform, but the "best" cases showed so little impairment of intelligence as measured by the tests employed that further inquiry into the functions of the frontal lobes was stimulated. Such investigations could be carried out substantially only in man because of the necessity for securing the maximum interplay of ideas between investigator and subject. Fortunately a sufficient number of patients have been studied now, before and after prefrontal lobotomy, to lend some weight to the hypothesis that was elaborated in the early stages of our[7] studies. Fundamentally, we believe that the frontal lobes subserve the functions of foresight and insight, particularly as related to the self. It is in relation to these ego functions that the affective coloring supplied by the thalamus is of overwhelming importance for the adjustment of the individual in his social milieu.

This report deals with some 300 patients who have been observed over a period of from 6 months to 9 years following prefrontal lobotomy. Emphasis is placed upon the social adjustment, in terms of working capacity and ability to live outside an institution. It also takes up the question of how much frontal lobe tissue must be sacrificed in order to eliminate the affective component that keeps the psychosis alive, and how much must be retained in order to preserve the ability of the individual to function adequately in the world of his fellows. Multiple operations have enabled us to form some opinions in regard to this all-important question, and the search for the "ideal" plane of section still goes forward. There is some hope that future investigations may make it possible to attack certain restricted areas of the brain for the relief of circumscribed ideational and behavioral abnormalities, such as hypochondriasis or obsessive-compulsive reactions. At the present time, however, we are inclined to operate on the working hypothesis that the results of operation depend upon the number of fibers severed in the anterior thalamic peduncle, and we endeavor to place the incisions so as to strike the proper balance between the abolition of the disabling psychosis and the preservation of capacity for productive work.

Operative Procedure. The surgical aspects of prefrontal lobotomy have been described.[9]

Burr holes are made through the coronal suture on each side about 6 cm. above the zygoma and are enlarged along the suture by means of a rongeur. The dura is then opened, hemostasis secured and the cortex punctured in an avascular area. The surgeon measures the diameter of the frontal lobes by passing a long cannula from one opening in the skull through the brain and out the other opening. At this location the frontal lobe varies between 4.5 and 5.5 cm. in diameter. The surgeon withdraws the cannula and angulates it downward delicately probing until he can positively identify the sphenoidal ridge. This gives an important landmark for precise surgery.

The surgeon removes the cannula and replaces it with a blunt knife inserting it to a depth 1 cm. short of the midline and then swinging it through an arc, first downward, then upward, through the frontal lobe. Here the surgeon relies constantly for orientation upon marks upon the scalp and upon guidance by the neurologist in order to remain accurately in the plane of the coronal suture. The ventricles can be entered without any harm. After irrigation of the incisions to control what little bleeding there may be, the surgeon returns the knife to the incisions, and by making radial thrusts or stabs, still under control by the neurologist, deepens the incisions to the base of

the frontal lobe, and as far as the midline. These stab incisions sever the white matter but displace the arteries on the mesial surface rather than lacerate them. Before closing the dura and scalp the surgeon finally injects a small quantity of iodized oil into the depths of the incisions, and after applying the dressing, marks on the bandage the location of the operative incisions underneath so that the technician may be able to take the roentgenograms as nearly as possible superimposing the burr holes in one of the stereoscopic lateral views. (Fig. 1.) An occipitofrontal view is also of value in order to indicate the depth of the incisions.

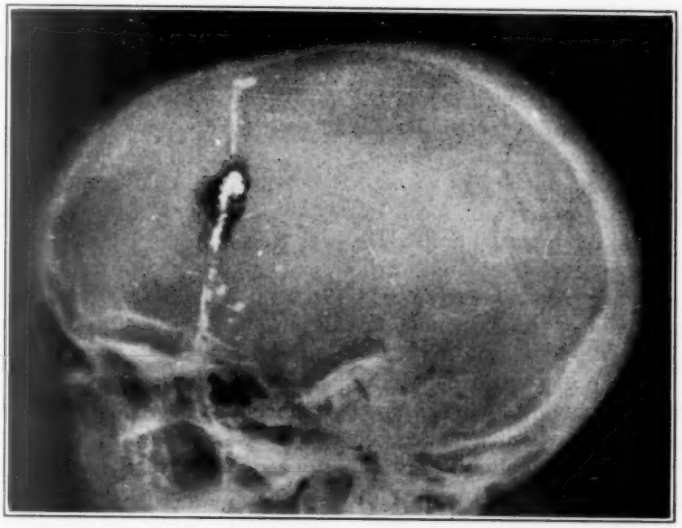

FIG. 1.—Roentgenogram after prefrontal lobotomy in plane of coronal suture outlined by iodized oil. Recovery from agitated depression after electroshock failed.

While incisions in the plane of the coronal suture yield good results in most cases of involutional depression or psychoneurosis, they are apt to be followed by only temporary improvement in schizophrenics. Relapses were so frequent, indeed, among our early cases that after many cases coming to secondary operation we arrived at a plan of fitting the incisions to the individual case. It requires precise surgery to cut the subcortical white matter in a plane, say, 8 mm. behind the coronal suture at the upper end and 5 mm. behind the sphenoidal ridge at the lower end, but it can be done, and its importance is stressed by the fact that deviations of 5 mm. one way or the other from the selected plane may make the difference between success and failure of the operation, or even death.

There are several factors that enter into the decision as to where to make the incisions in relation to the coronal suture. The most important of these is the duration of the psychosis. We conceive the psychosis in terms suggested by Egas Moniz, namely, the pathologic stabilization of synaptic patterns among various cell groups, particularly in the frontal lobes. With the development and fixation of the psychosis, we suggest that there occurs through the process of facilitation the inclusion of a progressively larger number of cortical cell population into the pattern of behavior. If this hypothesis is correct, it is likely that the spread of the abnormal stabilization is in a posterior direction, and that it comes to include mechanisms that are concerned in the ordinary everyday adaptations to social existence. Consequently, if the psychosis is of long duration and associated with

severe deviations from acceptable social behavior, the incisions must be placed so that the cell complexes underlying the dominant form of behavior can be cut off from their thalamic component. In other words the energizing emotional force in the psychosis must be cut down sufficiently to allow the other aspects of the personality to escape from dominance by the psychotic process. Prefrontal lobotomy fails in deteriorated cases largely because the operation cannot be carried out sufficiently far posteriorly to interrupt the psychosis without at the same time extinguishing those emotional factors that make for satisfactory adaptation in a normal social environment. A deteriorated schizophrenic looks and acts about the same with or without his frontal lobes.

Another factor in determining the location of the plane of the incisions is the age of the patient. In general older patients react more favorably to incisions placed anteriorly. In these cases, presumably, the behavior patterns of social existence have been stabilized for decades, and the psychosis is a development of the later period, so that a conservative operation produces sufficient reduction in the emotional toning of the psychotic process and still leaves the individual enough of the anatomic connections so that a good adaptation is possible. We have also been impressed with the large amount of frontal lobe that can be sacrificed in youthful individuals with eventual return to a satisfactory social adaptation. After severing the direct thalamic connections to a fairly large proportion of the frontal regions, there are still indirect connections that make for more adequate behavior after abolition of pathologic mechanisms persisting from the psychosis. Particularly interesting is the long continued process of adaptation in youthful individuals once the emotional nucleus of the psychosis has been eliminated. Improvement may be expected for at least 3 years and often more.

Contrary to our earlier conclusions, hypochondriasis and fixation of visceral complaints in involutional depressions have been satisfactorily overcome by a standard operative procedure, but a severe obsessive compulsive neurosis of long duration may require incisions from 5 to 7 mm. posterior to the plane of the coronal suture. Long-standing schizophrenia requires the maximum operation. In such cases we usually operate from above, through burr holes 10 to 15 mm. behind the coronal suture and 4 cm. from the midline, carrying the incisions down to the sphenoidal ridge or even angulating backward a little so as to reach the base of the frontal lobe 7 to 10 mm. behind the sphenoidal ridge. (Fig. 2.)

Emphasis is placed upon the variations in the procedure of prefrontal lobotomy because the success or failure of operation may depend upon a very few millimeters of tissue in the frontal lobe. We have reoperated upon some patients as long as 5 years after the primary intervention because of relapse into psychotic behavior. On the other hand, some patients have given every evidence of complete and permanent disability up to the present time several years after placement of incisions too far posteriorly. As stated previously, in order to obtain satisfactory results sufficient fibers must be severed in order to reduce the emotional component of the psychosis to the point where the ideas no longer dominate the behavior of the patient, yet the incisions must leave sufficient quantities of the frontal lobes in order to permit the patient to make a satisfactory adaptation in a social environment. Every millimeter that the incisions trespass upon the area posterior to the plane of the coronal suture renders this adaptation less complete and more difficult.

Certain aids in convalescence and rehabilitation have been described by us.[8] There are means of combating certain symptoms that have not been stressed previously. Convulsive seizures respond fairly well to a combination of phenytoin and phenobarbital in a dosage determined by the individual case. The medication should be continued until 2 years have

elapsed from the latest attack. Sometimes, however, 3 years may intervene between attacks. Urinary frequency and urgency with occasional incontinence have sometimes yielded to atropine and ephedrine in appropriate dosage. Inertia finds a suitable remedy in amphetamine sulphate in doses as high as 30 mg. daily. Electroshock therapy has been useful in mild relapses especially in the involutional depressions. Usually two or three shocks are sufficient to relieve the obsessive preoccupation in a way that was impossible previous to lobotomy. If the relapse is stubborn, however, reoperation is undertaken without delay. Weight control is a matter of calories and may require padlocks on the refrigerator. Amphetamine, however, not infrequently brings the appetite within bounds. This drug is also more useful than phenobarbital in the control of restlessness and irritability.

FIG. 2.—Roentgenogram after 2 prefrontal lobotomies, first in the plane of the coronal suture, second (4 mos. later) 1 cm. behind it. Patient was a violent tuberculous schizophrenic hospitalized for 5 years who subsequently gained 25 kg., healed in his tuberculosis and soon will be paroled to his family.

It goes without saying that patients who have been operated on are far from healthy, particularly at first. In undergoing prefrontal lobotomy they have exchanged one form of abnormal behavior for another. Whereas during the psychosis they have been too preoccupied with themselves, following operation they are at the mercy of every passing external stimulus. The emotional intensity characteristic of the psychosis gives way to the emotional shallowness of the postoperative state, and the imaginative activity which was at its height during the psychosis undergoes more or less permanent reduction. Patients who have made a satisfactory recovery, however, and this includes the majority of those operated on, are far from inanimate clods. They are cheerful, friendly, uncomplaining, outspoken, buoyant, for the most part. They fall in with the mood of their companions, are quick to follow suggestions and are not embarrassed, glum or self-conscious. They take an active interest in everything that goes on about them, read the papers, attend movies, work regularly and play games with intelligence and foresight. With them the emotional component of foresight and insight is sufficient for meeting external situations of moderate complexity. It seems, however, that introversial preoccupation is no longer possible. If asked about themselves and their previous

troubles they may recall various ideas or particular episodes, but without concern, and many patients have a more or less complete amnesia for the whole psychotic period that may be of many years' duration. This last fact was stressed particularly by Strecker, Palmer and Grant.[16]

Results. In Table 1 is given the present status of 260 patients who have been followed from 6 months to 9 years following prefrontal lobotomy, divided according to the main diagnostic groups. All of the patients have been seen or reported on during 1945. It will be seen that patients with psychoneuroses offer the best outlook as far as employment is concerned. These individuals are intelligent and possessed of a satisfactory energy component. Their difficulties in postoperative adaptation come from too great a tendency to aggressive behavior, which is gradually toned down in the years following operation. Patients with involutional depressions and psychoses achieve a satisfactory degree of relief from their painful ideas, but in many instances they have reached the age of retirement from business, or are no longer active in the management of the household. One patient, however, worked as a bookkeeper for 8 years following prefrontal lobotomy, and then, becoming bored with retirement after a few months, went back to work at her same job. Patients with involutional depression are very deserving of help by psychosurgery if other methods fail. Most of our cases in this category have either had previous shock therapy without relief, or because of physical complications have been considered unsuitable candidates. Prefrontal lobotomy is a remarkable therapeutic procedure for the relief of mental pain.

Table 1.—Status of Living Patients, June 1945, 6 Months to 9 Years Following Prefrontal Lobotomy

Disease	No.	Regularly employed, %	Partly employed, %	Keeping house, %	At home, %	In hospital, %
Involutional psychoses	83	10	6	43	25	16
Schizophrenias	96	29	9	8	28	26
Obsessive states	43	51	11	14	12	12
Psychoneuroses	35	46	3	26	20	5
Unclassified	3	67	..	..	..	33
Totals	260	30	8	22	23	17

Schizophrenia presents numerous problems that are far from solution. However, with every review of the schizophrenic patients undergoing prefrontal lobotomy we are more encouraged. It stands to reason that the results in terms of employability are inferior to those in the neurotic category, but the number of patients that are now at home after prolonged residence in mental hospitals is encouraging. Moreover a considerable number of patients are self-sustaining and with the lapse of time are improving rather than retrogressing. Prefrontal lobotomy is of particular value in the chronically disturbed and overactive schizophrenic as reported by several observers.[1] We now have several patients under observation at St. Elizabeths Hospital who were operated upon during the past 2 years. They were of the type that requires constant seclusion because of shouting, spitting, smearing and assaultive behavior. From 3 to 5 attendants were sometimes required to administer medicines and even food. Without good care these patients would have killed themselves through frenzy and exhaustion. These patients are now still in the hospital for the most part, but are clothed decently, eating with other patients, tractable and no longer troublesome or dangerous to the ward personnel. The saving to the hospital in wear and tear is considerable. One of the medical officers (W. W. Eldridge) is particularly gratified at the results in the disturbed tuberculous schizophrenics who represent an additional menace to their comrades and attendants

by spitting freely. Studies have shown that in these patients the postoperative period is characterized by a gain in weight up to 20 kg. and by progressive healing of the tuberculous process in the lungs.

Prefrontal lobotomy for the relief of pain is a subject that is under investigation. Patients have been operated upon successfully for the relief of tabetic pains, inoperable carcinoma, trauma to the cauda equina and thalamic syndrome. Relief of pain in phantom limb has been reported.[17] In these cases it would seem that the emotional component, the fear of pain, is vanquished, and that peace of mind is a big factor in the greater comfort secured by the patients.

Chronic alcoholism is not relieved by prefrontal lobotomy. Neither is epilepsy, although there are some reports of success in cases of dangerous epileptic furors and other complications of epilepsy.[15] Parkinsonism remains unchanged; in fact a patient has recently developed this disease 6 years after prefrontal lobotomy for an involutional depression at which time there was no hint of the disease. One patient with probable multiple sclerosis and severe emotional disturbances requiring hospitalization has been employed for a year and has shown improvement rather than advance of the disease.

Table 2 gives an estimate of the results of prefrontal lobotomy on the basis of 331 cases operated upon up to the present time. In estimating the results, the former condition of the patient has been kept in mind. For instance, a patient may be employed, and may be freed from his mental disturbance, but still be considered a poor result because of his inability to get along harmoniously with his relatives because of unleased aggressiveness that makes life miserable for them. On the other hand, a patient may still require hospital treatment but be considered a good result because of the cessation of disturbed behavior as described above. Some of the poor results stem from too limited an operation, with persistence of symptoms and no opportunity for further operation; some from operating upon patients whose deterioration had progressed too far to allow of a comeback under any known circumstances; and some from too extensive an operation, reducing the individual to permanent childish dependency,

TABLE 2.—RESULTS OF PREFRONTAL LOBOTOMY (SEPTEMBER 1936 TO JUNE 1945)

Disease	No.	Results: Good, %	Fair, %	Poor, %	Deaths,* %	Recent cases†
Involutional psychoses	108	50	31	16	3	10
Schizophrenias	126	46	36	16	2	25
Obsessive states	51	61	35	..	4	5
Psychoneuroses	38	63	29	8	..	3
Unclassified	8	25	12	25	38	
Totals	331	52	32	13	3	43

* Operative deaths only. Individuals dying subsequent to operation (18) have been listed according to results, good, fair or poor, during their postoperative term of life.

† Recent cases (shown by number) have not been included in the percentage tabulation.

On the whole, however, the good results outweigh the bad. Prefrontal lobotomy is a relatively safe operation, the operative mortality being under 3%, and it can be carried out in patients whose physical condition precludes other drastic forms of treatment.

Conclusions. Prefrontal lobotomy has been performed by us in 331 cases during the past 9 years. Refinements of the operative procedure have given us a controllable and accurate means of severing the thalamofrontal radiation in such a manner that in a high percentage of the cases the emotional component of the neurosis or psychosis can be reduced to the point of tolerability without sacrificing too much of the individual's ability to adapt himself to life outside an institution.

This surgical procedure is to be employed only in cases in which a favorable outcome is not to be anticipated under more conservative measures. It should not be postponed too long, however, since deterioration may progress to the point where operation will no longer be serviceable.

The most favorable results are obtained in obsessive tension states, with or without compulsions, in hypochondriasis and intractable psychosomatic conditions, and in agitated depressions. Less satisfactory results are obtained in schizophrenias, although as long as the patient is fighting his disease there still remains the possibility of satisfactory modification of his disturbed behavior. Alcoholism, paranoid states and psychoses with organic brain diseases yield rather poor results. The treatment of structurally conditioned painful disorders is giving favorable results.

The most important sequels are inertia, aggressiveness, and epileptic seizures, but these are disabling in only a minor percentage of cases.

About half the patients are usefully occupied, one-quarter remain at home and one-quarter are dead or institutionalized.

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SCRUB TYPHUS FEVER (TSUTSUGAMUSHI DISEASE) IN NEW GUINEA

REPORT OF 75 CASES

BY LIEUT. COLONEL THEODORE H. MENDELL, M.C., A.U.S.
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SCRUB typhus fever today is accepted as identical with Tsutsugamushi disease. It has assumed increasing importance in World War II because of its endemic presence in the Southwest Pacific area and the China-Burma-India theater. The disability and man power loss incurred by it make it a military problem of first rank. Reports gathered from the Southwest Pacific area show a mortality of 2 to 10%. In addition, a very small percentage of those who recover from the severe debilitating form of the disease frequently fail to regain sufficient stamina for general duty even after prolonged periods of convalescence. The minimal time a soldier can be returned to full duty after a moderate attack of scrub typhus fever is 30 to 60 days. In severe cases much longer periods of rest, 3 to 6 months, may be required to recondition the soldier.

Scrub typhus fever is a rickettsial disease caused by *R. orientalis* (*R. tsutsugamushi*). It results from the bite of a larval mite of the genus Trombicula, family Trombidiidæ, order *Acarina*, and cannot be communicated from man to man. In New Guinea these mites live in areas in which there are large "kunai grass" fields bordering on the jungle. In Japan the mite is called the "kedani mite" and the adult form flourishes along river beds, hence the name "Japanese River Fever." The larval form of the mite, responsible for transmission of the disease, feeds on vertebrates, requiring a blood meal from its host for development to the nymph stage. It becomes infected by feeding on the blood of an infected host. It is said to be able then to pass the disease on to succeeding generations. In New Guinea the rat and bandicoot, of which there are plenty, are the usual hosts; man only accidentally. In Malaya, India, China, Burma, Sumatra and Australia the most favorable habitat for the mite is the dense thick growth of "scrub" found along small streams in damp jungle common to these regions.

In September 1943 the Surgeon General, because of the increasing problem presented by scrub typhus fever, authorized the sending of an investigating team[2] to New Guinea. It found that the risk of infection seemed to be associated chiefly with kunai grass fields bordered by jungle along water courses. Such areas offered favorable environmental conditions for the growth and activity of the mite. The investigating team concluded that the risk was maximal during the first 4 to 6 weeks after an organization had occupied a camp site which had not been previously used or cleared, or when an organization engaged in combat was constantly moving into and occupying new areas. Of the cases investigated, 71% became infected within the first days after arrival of the unit in such an area, more than 90% occurred in the first 6 weeks; thereafter the incidence became sporadic. As camp areas were cleared and put in order, the risk of infection became progressively less. This we found to be especially true in this series of cases, as will be pointed out later.

The incubation period varies. There is no absolute information regarding its duration. It is usually stated as being 10 to 18 days, though the maximum period is unknown. In Oda's series of 14 cases, cited by Strong,[4] whose contacts could be definitely traced, the incubation period varied from 7 to 12 days and averaged 9 days from the time of the bite to the onset of symptoms. On only 1 case of this series was the exact period of incubation computable. One soldier, whose squad had bivouacked on patrol duty in an area from which typhus originated, was relieved and sent to the rear where

TABLE 1.—CLINICAL SUMMARY OF 75 CASES OF SCRUB TYPHUS FEVER

	Temperature											System involvement						
	Ht.	Days duration	Lysis or crisis	Pulse	Eschar (location)	Rash	Adenopathy	Splenomegaly	Conjunctivitis	Epistaxis	Deafness	Nerv.	Pulm.	C.V.	W.B.C.	Agglutination OXK	Rec.	Died
1.	105°	21	C	90	Axilla	+	+	+	+	−	−	−	+	−	10,000	1:1280	+	
2.	106°	12	..	120	Loin	+	+	+	+	−	+	+	+	+	6,400	0		+
3.	104°	20	L	100	....	−	+	+	+	+	−	+	−	−	7,000	1:80	+	
4.	104°	8	C	86	....	−	−	+	+	−	−	−	−	−	4,800	1:160	+	
5.	105°	23	L	120	Axilla	+	+	+	+	−	+	+	+	−	6,000	N.D.	+	
6.	102°	18	L	90	Face	−	+	+	+	−	+	+	+	−	8,000	1:160	+	
7.	103°	20	L	84	Scrotum	−	+	−	+	−	−	−	−	−	11,000	N.D.	+	
8.	104°	10	C	88	Thigh	−	−	−	+	−	−	+	−	−	9,000	N.D.	+	
9.	103°	15	L	92	....	−	+	−	−	−	−	+	+	−	8,700	N.D.	+	
10.	102°	17	L	100	Ankle	+	−	−	+	−	−	−	+	−	N.D.	N.D.	+	
11.	102°	27	L	94	....	+	+	−	−	−	−	−	+	−	6,400	1:160	+	
12.	104°	31	L	96	....	+	+	+	+	−	+	−	+	−	10,200	N.D.	+	
13.	104°	27	L	94	Ankle	+	+	−	−	−	+	+	−	−	6,500	1:160	+	
14.	102°	28	C	88	....	+	+	+	−	−	+	+	−	−	4,800	N.D.	+	
15.	105°	29	L	94	Leg	−	+	−	−	−	−	−	−	−	5,100	N.D.	+	
16.	104°	15	L	88	Knee	−	+	−	−	−	+	−	−	−	6,500	N.D.	+	
17.	104°	29	C	96	....	+	+	−	+	−	+	−	−	−	5,300	N.D.	+	
18.	104°	13	C	92	Popliteal space	+	+	+	+	−	+	−	−	−	9,700	1:40	+	
19.	104°	17	C	96	Calf	+	+	−	+	−	−	−	−	−	5,100	N.D.	+	
20.	103°	19	C	88	....	+	+	−	+	−	+	+	−	−	8,000	1:80	+	
21.	103°	7	C	84	Heel	+	+	−	−	−	+	−	+	−	8,700	1:640	+	
22.	102°	14	L	86	....	+	+	−	−	−	−	−	+	−	3,800	1:80	+	
23.	103°	12	L	94	Forearm	−	+	+	−	−	+	−	−	−	8,000	1:80	+	
24.	104°	10	L	96	Thigh	+	+	−	−	−	−	−	−	−	7,100	N.D.	+	
25.	103°	14	C	104	Sacrum	+	+	−	+	−	−	−	−	−	4,300	1:160	+	
26.	104°	16	C	108	Ankle	+	+	+	+	−	+	+	+	−	8,600	N.D.	+	
27.	104°	22	L	96	....	+	+	−	+	−	−	+	−	−	6,300	N.D.	+	
28.	106°	9	L	102	Ankle	+	+	+	−	−	+	+	−	−	8,000	N.D.	+	
29.	104°	20	L	108	Arm and thorax	+	+	+	−	−	−	+	+	−	8,300	N.D.	+	
30.	105°	16	L	96	Leg	+	+	+	+	−	−	+	+	−	7,000	N.D.	+	
31.	104°	14	L	98	Scrotum	+	+	−	+	−	−	−	−	−	8,100	1:80	+	
32.	104°	12	C	90	....	+	+	+	+	−	−	−	−	−	7,800	1:80	+	
33.	104°	22	L	96	Loin	+	+	−	+	−	−	−	+	−	5,600	N.D.	+	
34.	105°	23	C	96	Axilla	+	−	+	+	+	−	−	−	−	11,000	N.D.	+	
35.	105°	14	C	100	Axilla	+	−	+	+	−	−	−	−	−	6,000	0	−	
36.	105°	15	L	102	Groin	+	+	+	+	−	−	−	−	−	6,000	0	−	
37.	102°	17	L	98	Axilla	+	+	−	+	−	−	−	+	−	5,500	N.D.	+	
38.	104°	21	C	100	Scrotum	+	+	−	+	−	−	−	+	−	8,500	N.D.	−	
39.	104°	21	C	100	Scrotum	+	+	−	+	−	−	−	+	−	5,500	N.D.	+	

29.	104°	26	L	96	Leg	+	+	+	+	−	−	−	−	−	8,100	1:80	+
30.	105°	16	L	96	Scrotum	+	+	−	+	−	−	−	−	−	7,800	1:80	+
31.	104°	14	L	98	....	+	+	+	+	−	−	−	−	−	5,600	N.D.	+
32.	104°	12	C	90	Loin	+	+	−	+	−	−	−	+	−	11,000	N.D.	+
33.	104°	23	L	96	Axilla	+	+	+	+	+	−	+	+	−	4,000	1:80	+
36.	105°	13	C	100	Axilla	+	−	+	+	−	−	−	−	−	6,000	0	+
37.	105°	15	L	102	Groin	+	+	+	+	−	+	−	+	−	8,500	N.D.	+
38.	102°	17	L	98	Axilla	+	+	−	+	−	−	−	+	−	5,500	N.D.	+
39.	104°	21	C	100	Scrotum	+	+	+	+	+	−	+	+	−	12,000	1:40	+
40.	105°	30	L	112	Axilla	+	+	+	+	−	−	+	+	−	7,800	0	+
41.	104°	19	L	102	Forearm	+	+	−	−	−	+	−	−	−	N.D.	1:160	+
42.	105°	14	L	106	Leg	+	+	−	−	−	−	−	+	−	5,800	N.D.	+
43.	104°	22	L	98	....	+	+	+	+	−	−	+	−	−	4,150	1:40	+
44.	103°	9	C	82	Scrotum	−	+	+	−	−	−	−	+	−	11,500	N.D.	+
45.	103°	11	L	86	Ankle	+	+	+	−	−	−	−	−	−	12,500	1:40	+
46.	102°	19	L	90	Axilla	+	+	+	+	−	−	+	−	−	8,000	1:640	+
47.	103°	9	L	88	....	+	+	−	−	−	−	−	+	−	7,150	1:640	+
48.	103°	16	L	90	....	+	+	+	+	−	+	−	+	−	11,600	N.D.	+
49.	105°	8	C	88	Arm	+	+	−	+	−	+	+	+	−	4,700	1:40	+
50.	105°	34	L	112	Both axilla	+	+	−	+	−	+	−	−	−	9,300	N.D.	+
51.	104°	25	L	110	....	+	+	+	+	+	−	+	+	−	5,200	N.D.	+
52.	105°	17	L	112	Thigh	+	+	−	+	+	+	+	−	−	11,000	N.D.	+
53.	104°	19	L	96	....	+	+	−	+	−	−	−	−	−	8,000	N.D.	+
54.	104°	15	C	104	Popliteal space	+	+	+	+	−	+	+	+	−	8,100	1:80	+
55.	105°	16	L	96	Thigh	+	+	−	+	−	−	+	−	−	12,000	N.D.	+
56.	105°	16	L	98	Buttock	+	+	−	−	+	−	+	+	−	N.D.	N.D.	+
57.	104°	35	L	108	....	+	+	+	+	−	−	+	+	−	8,100	N.D.	+
58.	103°	10	C	96	....	+	+	−	+	+	−	+	−	−	10,000	N.D.	+
59.	105°	14	L	92	....	+	+	−	+	+	−	−	+	−	6,000	1:80	+
60.	104°	19	L	100	....	−	+	+	−	−	−	−	−	−	4,750	1:160	+
61.	102°	15	L	94	Axilla	−	+	+	+	−	+	−	+	−	6,700	N.D.	+
62.	104°	16	L	96	Loin	+	+	−	+	+	+	−	+	−	9,500	N.D.	+
63.	104°	14	L	104	Groin and shoulder	+	+	−	+	−	−	−	+	−	N.D.	N.D.	+
64.	104°	10	L	116	Axilla	+	+	+	−	−	−	+	−	−	4,000	1:40	+
65.	104°	7	C	82	Both legs	−	+	+	+	−	+	+	−	−	10,500	1:80	+
66.	104°	13	L	100	Arm and thorax	−	+	−	−	−	−	+	−	−	6,800	N.D.	+
67.	104°	25	L	100	....	+	+	+	+	−	−	+	+	−	4,800	N.D.	+
68.	105°	18	L	106	Scrotum	+	+	+	+	−	−	−	+	−	5,500	N.D.	+
69.	104°	13	L	102	Ankle	+	+	−	+	−	−	−	−	−	4,000	N.D.	+
70.	102°	17	L	88	....	+	+	+	+	−	+	+	−	−	6,000	N.D.	+
71.	104°	15	..	90	....	−	+	−	+	−	−	+	+	+	6,700	1:80	+
72.	104°	16	L	92	Knee	−	+	−	+	−	−	−	+	−	8,000	1:40	+
73.	103°	11	L	88	Scrotum	+	+	−	−	−	−	−	−	+	9,000	N.D.	+
74.	104°	24	L	100	....	−	+	+	+	−	+	+	+	−	7,950	1:640	+
75.	105°	11	L	102	Scrotum and penis	+	+	−	+	−	−	+	+	−	7,500	1:160	+

there were no typhus mites. He contracted the disease 21 days after exposure. There is no telling how many days prior to leaving the area he had been bitten, hence no standard was available for estimating the time elapsing between the bite and the onset of symptoms. The minute size of the offending mite, the painless nature of the bite, the prevalence of skin affections in the tropics, all tend to make the soldier overlook or place no significance upon the eschar. Frequently, when the lesion was pointed out, he stated he had been unaware of its presence. If he had recognized it, then he had little knowledge of its date of appearance.

Clinical Features of the Disease. The classical picture of scrub typhus fever as was seen here is that of a soldier being stricken suddenly, without warning, with chills and fever, the temperature rising quickly to 103° to 106° F. within 48 hrs. There was invariably a history of exposure to kunai grass in the jungle. Prostration, sweats, malaise, anorexia, joint pains, hyperesthesias, tinnitus soon ensued; occasionally epistaxis, frequently temporary deafness. An eschar, pathognomonic lesion of the disease was usually present from the onset, often requiring careful search of the entire body to disclose. The lymph glands were enlarged and tender, more so in that region of the body draining the eschar. Within 4 to 8 days a macular mulberry rash, non-petechial, appeared over the thorax spreading to the extremities and face, usually subsiding about the 10th to the 12th day. The spleen, always enlarged, was frequently palpable. Leukopenia with relative lymphocytosis was usual, a normal white blood cell count often occurred, leukocytosis was rare unless secondary infection intervened. There was no anemia. In more severe cases, after about 1 wk., nervous, pulmonary and to a lesser extent cardiovascular system involvement appeared. The temperature was continuous early, then became remittent or intermittent, subsiding as a rule by lysis between the 10th and 20th days. The pulse was slow in proportion to the temperature. The Weil-Felix reaction with OXK strain of *Bacillus proteus* when positive occurred after the 10th day in dilutions of 1:80 or above. It was negative for OX_{19} and OX_2 strains. In a few cases the agglutination remained persistently negative. The peak of the titer usually occurred during the convalescence. Marked weight loss and asthenia always followed the acute phase of the disease which required long periods of rest and reconditioning before restoration to duty. With the exception of 2 cases, all recovered completely in spite of stormy courses.

Report of 75 Cases Presented. Seventy-five cases have been analyzed and are presented from a series of 87 diagnosed scrub typhus fever over a 3-month period, August-September-October, 1944, while this hospital was stationed in a combat area in north New Guinea where the disease is endemic. Twelve cases have been excluded from this report because they did not absolutely meet the required criteria for a diagnosis, although typhus fever was the most likely explanation of their symptoms. All 12 recovered and were discharged to duty after short periods of convalescence. Of the 75 cases there were 2 deaths, a mortality of 2.7%, which compares favorably with the rate of 2 to 10% quoted for this theater.[2] In addition, there were 6 cases admitted during this period for post-typhus asthenia in men who had had typhus fever from which they had recovered months previously and had been returned to duty. They were not able to keep up with their fellow soldiers, lacking sufficient stamina, and had to be returned for further periods of rest which finally restored them to full health. These 6 cases serve to emphasize the prolonged convalescence required to rehabilitate the soldier following a severe attack of scrub typhus.

Of the 75 active cases herein reported, 58 occurred during the first 6 weeks of the 3-month period while combat and operations were at their height. During

the next 6-week period, after camp sites had been cleared of grass and scrub, and operations and movements had virtually ceased except for patrol duties, the incidence dropped remarkably, only 17 cases occurring. After that typhus fever disappeared from the admission list. This experience is in keeping with that reported by the Surgeon General's investigating team.

Age is an important factor in the prognosis. As a rule, the younger the individual the less severe the illness, and correspondingly less the mortality rate. It has been shown among civilian populations the mortality rises sharply to as much as 15 to 50% after age 40. One of our 2 deaths occurred in a soldier aged 33 years. Sixty-three of our cases occurred below the age of 30 years, of which 51 were below the age of 25; undoubtedly an important factor in the low mortality rate.

All our patients gave a history of having been exposed to kunai grass in the jungle for periods varying from 2 to 60 days. Fifty-six had slept on the ground in the grass areas, several slept in the scrub during operations and most of the remainder stated they had been on work details cutting, hauling away or burning the grass and scrub.

Fever is a universal finding in this disease. It is rarely under 102° F. and more usual at levels of 104° to 106°. In no case did the temperature endure less than 7 days, the longest was 34 days. Seven cases ranged between 7 and 10 days; 46 (61%) between 10 and 20 days; 18 (24%) between 20 and 30 days; and 4 cases more than 30 days. In 52 cases the temperature reached normal by lysis, in 21 by crisis; 2 died.

The *pulse rates* were slow compared to the temperature curves, 80 to 100 per minute being the usual finding. This is fairly characteristic. Rapidity of the pulse is a guide of oncoming circulatory insufficiency.

The *eschar* is the pathognomonic telltale lesion of the disease. Once seen, the observer will never mistake its presence or significance in the next case. It is so typical that the diagnosis in its presence, with a symptomatology suggesting the disease, can be made regardless of laboratory findings. It appears as a small ulcer, 0.2 to 1 cm. in diameter, circular or oval, resulting from the bite of the larval mite, with a raised reddened areola surrounding it, covered by a black necrotic scar which is shed after a few days leaving a definitely punched out ulcer with a depth of 1 to 2 mm. The mite prefers warm, moist regions of the body, hence selects the axilla, groin, scrotum or belt line to bite. There may be multiple eschars in the same individual.

Fifty-one patients (68%) demonstrated the typical eschar; in 7 eschars were multiple, 6 of whom had 2 and 1 had 3. The majority were located in the axilla, scrotum and groin. In some cases only a careful thorough search of the skin surface yielded the lesion. A small one can be missed easily especially if located in a hidden fold or overlapping fold of skin as occurs in a relaxed scrotum.

The *rash* occurred in most cases between the 4th and 8th days, fading within 2 to 6 days following appearance. It is macular, spoken of as mulberry hue, nonpetechial, covers the trunk, extremities and to a lesser extent the face. It was present in 59 cases (78%). Most of the other cases were admitted late and it is possible they demonstrated the rash early which could have been overlooked. In some cases the rash may be so fine that unless the daylight is bright it can be missed. However, this is not usual.

Adenopathy is an almost universal finding. It is usually generalized. Seventy-one patients (95%) demonstrated enlarged, tender lymph glands. The regional glands draining the eschar are always larger and more tender than the others, although the others share in the process. With eschars in the groin, scrotum or lower extremities and the patients lying flat in bed without a pillow, the inguinal glands are often visibly elevated above

the skin level. In severe cases the enlargement may reach the size of a plum. They offer no problem in therapy, never suppurate and subside with recovery.

Splenomegaly occurred in 37 cases. It is a soft, smooth edged spleen not larger than 2 fingerbreadths below the costar margin. While the finding of a palpable spleen is not of too much importance in a malarious area, nevertheless it is always enlarged in scrub typhus fever, whether palpable or not.

Conjunctivitis is a very frequent finding. The intensity of the conjunctivitis usually was proportional to the toxicity and severity of the infection. In many, it was so marked that subconjunctival hemorrhage occurred. It is more an episcleritis originating upon the lid conjunctiva and extending forward over the sclera toward the cornea, decreasing in intensity as it reaches the cornea. There may be accompanying conjunctival separation by edema. Its type is rather peculiar to the disease, is not met with in other diseases with the possible exception of Weil's disease. Fifty-three patients (71%) presented this form of conjunctivitis. All cleared with recovery, leaving no residual signs. One patient who had severe conjunctivitis developed diminished vision in one eye during convalescence, but this was regarded to be due to nerve involvement.

Epistaxis occurred in 9 cases (12%) somewhat less than is usually stated. It offered no therapeutic problem, only 1 patient required packing to control bleeding.

Tinnitus occurred in 36 cases and *deafness* in 26 (35%). The tinnitus was transitory and gave no trouble. The deafness, when present, usually endured throughout the fever period, spontaneously disappearing with normal temperature. While it produced some degree of anxiety in some, most patients were so toxic and apathetic that they were unaware of their decreased auditory powers. In only 1 case did it endure for a 30-day period beyond recovery.

Systemic Involvement. Involvement of the *nervous system* is a frequent finding. When one views the diffuse encephalitis at autopsy, one is surprised that clinical signs of brain involvement do not occur in all cases. Headache, apathy, prostration, hyperesthesias, dizziness occurred in all; tinnitus, deafness, neck pains, tremors, mental confusion and delirium in a large number. Such findings could well be present in any severe septic or toxic state. Therefore, unless definite positive neurologic signs were elicited or convulsions or psychotic manifestations present, clinical nervous system involvement was not diagnosed.

There were 36 patients (48%) with involvement of the central nervous system during the course of their disease. Usually this appeared toward the end of the 1st week and persisted throughout the fever stage. All except 3 made complete recoveries; the 2 who died and 1 who developed a severe post-typhus psychosis for which he had to be evacuated. It was later learned he recovered. There were 2 other patients who developed postinfectious psychosis during the convalescent period; one lasted several days and the other 1 week. Both had to be restrained, but recovery was complete.

Lumbar puncture was required and done in only 1 patient. His headache, neck signs and positive Kernig sign were so severe on admission that meningitis had to be considered. Seventy-one cells, 90% of which were lymphocytes, were found in the spinal fluid. Pleocytosis not infrequently occurs in this disease due to the diffuse encephalitis. Upon recovery of this patient, a second tap disclosed normal findings with 5 cells. No other case required lumbar tap. As a therapeutic measure to relieve pressure, this procedure has not been found of great value by others. We experienced no need for it on this score, and it is felt the patient should be spared any upsetting measures if their value is questionable.

The *lungs* were involved in 38 patients (51%). The more severe the infection,

the more likelihood of the presence of a rickettsial pneumonia or pneumonitis. Ahlm and Lipshutz[1] reported 67% of their cases had atypical pneumonic signs at the height of their illnesses. Every one of our patients manifested cough, chest pain, dyspnea, expectoration at some time during the course of his illness, but unless definite pulmonary signs could be elicited, clinical pulmonary involvement was not diagnosed. Twenty of the 38 patients had a typhus pneumonitis, fairly diffuse, bilateral, manifested by parenchymatous crepitant râles, areas of impairment, limited breathing and altered breath sounds. Eighteen had severe bilateral bronchitis and bronchiolitis characterized by cough, expectoration, occasionally bloody, with rhonchi, sonorous and wheezing râles in the larger and smaller bronchi. The lung signs in all disappeared with recovery except in the 2 cases who died. Roentgen ray film being a critical item in a forward area, routine chest plates were not taken except in 2 instances. One showed a bilateral infiltrative lobular pneumonitis, and the other a similar pneumonitis with a unilateral atelectasis. There is really no need for roentgen ray examination of these patients, and it is better not to disturb them unduly in a disease wherein rest is so vital.

There is no treatment necessary for typhus pneumonia unless secondary infection complicates. Occasionally the cough may be distressing and require sedation. Otherwise the lung findings are reversible to normal with recovery.

Involvement of the *cardiovascular system* occurred in only 3 cases, 2 of whom expired with some degree of congestive failure, the other developing arrhythmia alternating with gallop rhythm during the fever stage. The latter made a complete recovery. In all cases the blood pressure was decreased, hypotension was a constant finding in the sick, prostrated patient. Pressures of 90 to 70 mm. mercury (systolic) and 60 to 40 mm. mercury (diastolic) were usual. Some observers have stated that sodium chloride administration tended to stabilize the blood pressure level. With recovery, however, the blood pressure returns to normal. Rarely there is some mild peripheral failure associated with the hypotension and generalized vasiculitis, but not enough occurred on this series to cause any alarm. In some of the latter instances, plasma was tried but seemed not to affect the situation.

The *peripheral blood picture* is that of a leukopenia with a relative lymphocytosis. Counts of 10,000 were unusual, the highest total count observed was 12,500. A leukocytosis may indicate complicating bacterial infection. Anemia is not associated with the disease. If it be present, another cause should be sought.

The *Weil-Felix* reaction is of great aid in making the diagnosis in doubtful cases. It must be stated, however, that in a small percentage of cases it may remain persistently negative. In most cases there is usually a positive agglutination in titers of 1:160 or more with OXK strain of *Bacillus proteus* and a negative agglutination with the OX_2 and OX_{19} strains. The degree of positivity with OXK is by no means proportional to the severity of the disease. Three of our sickest patients had zero agglutination throughout their illnesses and convalescence; 1 death had a zero agglutination, and the other only 1:80. Some writers have explained such low titers in fatal cases as a failure of the body forces to manufacture antibodies. This is not an established fact, however. The mildest case, with fever for only 7 days, had an agglutination of 1:60.

In this series, the clinical findings were correlated in every case with the titer of the agglutination. While others speak of 1:160 or above as being a positive Weil-Felix for OXK, still others have found 1:80 significant especially if demonstrated in rising titer. The titers of 1:80 or higher among our patients were the result of several tests performed a week apart after the 2nd or 3rd week of illness. The original reaction was usually negative or lower in titer. In many of the lower

titers obtained, the presence of the eschar or classical clinical features of the disease, or both, rendered the diagnosis undoubted in spite of the low Weil-Felix agglutination. In the report of Ahlm and Lipshutz, of 57 agglutinations performed, 21 were negative or 1:80 or less in proven cases of scrub typhus.

As we were stationed in a forward area of combat, our supply of antigen was limited and soon ran out. It was decided, therefore, not to do the test in cases with eschars in which the diagnosis was evident, but only in cases in which the diagnosis was in doubt and wherein the clinical findings were not conclusive. Many cases fell into the latter group, demonstrated negative agglutinations and do not appear in this report. In that sense the negative agglutination proved of value in eliminating the diagnosis. Later in this study, we received a small replacement supply of antigen and were able to be a bit more liberal in performing the Weil-Felix test.

The agglutination test was performed in 34 patients of this series, in many at least twice to demonstrate rising titers. Eight patients had titers of 1:40, of whom 7 had eschars and all 8 demonstrated the clinical features of the disease. Twenty-three patients had agglutinations of 1:80 or above, of whom 12 had eschars, and in all 23 the diagnosis was beyond question. Three patients, 1 of whom died, with typical eschars and clinical symptomatologies had zero agglutinations. It is worth repeating, that whereas a positive agglutination of 1:160 or more with OXK strain of *B. proteus* is very valuable in establishing the diagnosis, the disease picture is so definite, rendering itself so readily to diagnosis in areas wherein it is endemic, that an agglutination is not absolutely necessary to the clinician except in doubtful cases. Therefore, for an Army Hospital in the field not equipped to do such a laboratory procedure because of lack of supplies or trained personnel, diagnostic accuracy should not be seriously handicapped.

Isolation of the rickettsia from the patient's blood was not attempted. However, this procedure is easy of performance and can be of great value.

The *pathologic anatomy* of scrub typhus fever is that of a vasculitis and perivasculitis of the smaller vessels involving chiefly the reticulo-endothelial system, brain, lungs and heart. The picture is best presented by the following two autopsies performed upon the 2 patients who died.

Case 1. Male, white, age 23, infantryman, was admitted to this hospital on Aug. 14, 1944, with a diagnosis of dengue. His illness began suddenly on August 6, with chills and quickly mounting temperature to 104° F. daily. The diagnosis was changed to scrub typhus fever on August 16. He had served in a combat operation in the jungle, had slept on the ground in the kunai grass area, but had no knowledge of having been bitten by a mite or other insect. He complained of profuse sweats, headaches, dizziness, malaise, joint pains, anorexia, tinnitus and deafness. He had generalized aches and was exquisitely tender over his limbs. No eschar was found, but adenopathy was generalized and the glands were tender and soft. Conjunctivitis was marked. He soon developed circumoral twitchings, mental confusion, and delirium. Nuchal rigidity and bilateral positive Kernig signs were present; the last 2 days before death he developed generalized convulsions. The lungs exhibited a diffuse, bilateral pneumonitis. Blood pressure range averaged 80/60 mm. of mercury. The temperature ranged between 100° in the morning to 105° and 106° in the evening. The leukocytes were 6700 and relative lymphocytosis was present. Weil-Felix reaction with OXK was 1:80, negative with OX_2 and OX_{19}. He died on August 21, 15 days after onset of illness.

Clinical Diagnosis. Scrub typhus fever with terminal cerebral involvement.

Postmortem Examination (Capt. Henry Brody, M.C.). Body is that of a white male, 167 cm. long, estimated weight 135 lbs. Conjunctivæ are injected and slightly chemotic. Right axillary lymph nodes are enlarged, those in left axilla palpable. Scattered over trunk both anteriorly and posteriorly and extending to a lesser extent to the neck and upper portions of the lower

extremities, are innumerable vesicles varying in size from a pin head to almost 5 mm. in diameter. The fluid in all but one of the vesicles is clear, that on smear yielded staphylococci. Small shotty lymph nodes are present in both inguinal regions. Careful examination of the entire external aspect of the body reveals no ulcerated lesion or eschar.

The panniculus is scant. The muscles of chest and abdominal walls are exceedingly dry and a deep red. Abdominal organs are normally disposed, and peritoneal surfaces smooth and glistening. The liver edge is 3.5 cm. below the xiphoid in the midline. The spleen is enlarged but entirely within the costal border. The domes of the diaphragm are at a level of the 4th rib on the right and the 6th on the left. The thymus is small, the pleural cavities contain no fluid. Adhesions are present at the right apex. The pericardial cavity contains about 30 cc. of clear yellow fluid.

The heart is of normal size and shape. The ventricular cavities are slightly dilated, the myocardium is slightly flabby. On incision, the myocardium shows a faint mottling, with yellow brown and brownish red areas alternating. No scars or focal lesions seen. The endocardium is smooth throughout. The valves appear normal. Except for a single tiny atheromatous plaque close to the mouth of the left coronary artery, the coronary arteries are not remarkable.

The lungs are voluminous. On the right adhesions bind the pleura to the parietes. A small amount of fibrin is loosely adherent to the pleura at several points. Otherwise, the pleura is smooth and glistening. The dependent portions of both lungs are deep purple as contrasted with the light pink of the upper portions. The dependent portions are boggy but without areas of consolidation. On section these portions are deep purple, moderately wet, with a small amount of bloody fluid pouring from the surface. The upper lobes show some areas of slight congestion, but for the most part are pink and air containing. Anthracotic markings are minimal. No pneumonia is recognized. The bronchial mucosa is hyperemic, and a few of the larger ones contain a little frothy fluid which is blood tinged. The pulmonary vessels show nothing unusual. Their endothelial lining, as far as could be traced, shows no gross visible damage. The hilar and mediastinal lymph nodes are not appreciably enlarged.

The spleen is between 3 and 4 times normal size, estimated to weigh about 350 gm., measuring 16 x 11 x 9 cm. The capsule is smooth and tense. On section, the Malpighian bodies, which are small, stand out clearly against the soft, deep purple pulp. The pulp can be scraped away with a knife. No pigmentation, infarcts or necrosis are seen.

The right kidney measures 19 x 7.5 x 4 cm., the left 14 x 8 x 5.5 cm. Their capsules strip with ease, leaving a smooth surface. The cut surface shows normal markings. The calyces and pelves are normal. Both renal arteries and ureters are normal. The suprarenals are small and thin, on section they appear rather poor of lipid content. The urinary bladder is distended with urine, the epithelial surface is pale, there are no diverticulæ. The trigone is not remarkable. The prostate is small. The seminal vesicles, epididymes and tests all appear normal.

In the lower third of the esophagus, a small bleb, similar to those seen on the skin, is found. The stomach and intestinal tract are not remarkable. The mesenteric lymph nodes are slightly enlarged. The liver appears larger than normal, measuring 29 x 19 x 10 cm. The capsule is smooth, the cut surface shows slight congestion with fine, distinct architectural marking. The gallbladder contains 25 cc. of thick brownish green bile. The cystic, hepatic and common ducts are normal. A lymph node measuring 3 x 1.5 x 0.5 cm. is present close to the Heisterian valve. The pancreas is normal. The thyroid is small, its cut surface pale and glossy. The blood-vessels show practically no atherosclerosis, as is also true of the larger branches. The venous and portal systems are normal.

The brain appears large and there is some slight increase in subarachnoid fluid. The pial vessels are slightly engorged. No hemorrhages, petechiæ or areas of exudate are found. On section, after fixation, many of the pial vessels are distended with firm clot. Similarly, small vessels throughout the substance of the brain are distended. No striking anatomic distribution is recognized, though they are somewhat more numerous in the basal ganglia, bilaterally, than elsewhere. The ventricles are not dis-

tended. No areas of necrosis or hemorrhage are found.

Histologic Study (Capt. Emmett B. Settle, M.C.). The heart sections show characteristic acute focal and diffuse myocarditis. Acute serous pericarditis is also present. Sections of the aorta show minimal perivascular mononuclear infiltration about the vasa vasorum. The lung sections show characteristic acute primary interstitial pneumonia with vascular inflammation and damage, hemorrhage and acute congestion with edema. Other sections show an acute secondary bronchiolitis with acute secondary lobular bronchopneumonia. An acute serous pleuritis is present. The spleen shows characteristic acute splenitis with congestion and hemorrhage. The lymph node sections show characteristic acute adenitis with congestion, hemorrhage and focal necrosis. The stomach is essentially normal, there is a mild vasculitis and perivasculitis. The adrenal sections show interstitial clumps of mononuclear cells of the medulla and vascular zones. The kidney sections show characteristic acute focal interstitial nephritis with mononuclear infiltration. The renal tubular epithelium shows cloudy swelling. Sections of the testicles show mild perivascular mononuclear infiltration with interstitial edema. Physiologic stage of involution is seen in the thyroid. Sections of the skin show mild perivascular mononuclear infiltration about the capillary loops of the papillary bodies as well as the deep and superficial network of the corium. Sections of the brain show vasculitis and perivasculitis with an occasional nodule and punctate hemorrhage. Some sections show a mild serous leptomeningitis. The liver specimen was not received.

Pathologic Diagnosis. 1. General: (*a*) Tsutsugamushi disease (scrub typhus).

2. Cardiovascular System: (*a*) Vasculitis and perivasculitis, acute generalized, minimal to moderate. (*b*) Myocarditis, acute focal and diffuse, mild. (*c*) Pericarditis, acute serous mild.

3. Respiratory System: (*a*) Pneumonia, acute primary interstitial, severe. (*b*) Pleuritis, acute, serous, mild. (*c*) Bronchopneumonia, acute, lobular, secondary, mild. (*d*) Bronchiolitis, acute, purulent, mild.

4. Spleen and Hematopoietic Tissues: (*a*) Splenitis, acute with congestion, hemorrhage and splenomegaly. (*b*) Lymphadenitis, acute, with congestion, hemorrhage, focal necrosis and lymphadenopathy.

5. Gastro-intestinal Tract: Normal.

6. Genito-urinary System: (*a*) Nephritis, acute, focal, interstitial, mild. (*b*) Cloudy swelling of renal tubular epithelium. (*c*) Orchitis, acute interstitial, mild.

7. Central Nervous System: (*a*) Encephalitis, acute focal, mild, with congestion, edema and focal hemorrhage. (*b*) Leptomeningitis, acute serous, minimal.

Case 2. Male, white, age 33, infantryman, was admitted on Oct. 22, 1944, for cough, soreness in chest, chills, vomiting and temperature of 104° F. His illness began 7 days previously with fever, sudden in onset. He had been on advance patrol duty which took him far into the jungle, where he had been exposed to kunai grass and scrub for several weeks. He was extremely toxic; there was a scattered erythematous macular rash present over back, arms and shoulders. An eschar 1 cm. in diameter with a black necrotic covering was present over the right postero-lateral lumbar area. The lymph glands were all enlarged and tender, more so in the inguinal regions. The spleen could not be felt. Conjunctivitis with subconjunctival hemorrhages were intense. There was a bilateral extensive lobular pneumonitis, nuchal rigidity, positive Kernig, tremors and mental confusion. The course was rapidly downhill, toxicity and prostration were profound, temperature remained between 104° and 106° F. daily, blood pressure 58/40. On the 12th day of the disease the Weil-Felix reaction with OXK was zero. The leukocytes were 6400 with 52% lymphocytes. On the 13th day, oliguria appeared which developed into complete anuria, the non-protein nitrogen rose to 100 mg. per 100 cc. On the same day, acute congestive cardiac failure appeared which was quickly digitalized. He expired on Oct. 30, 1944, the 15th day of his illness.

Clinical Diagnosis. Scrub typhus fever.

Postmortem Examination (Capt. Henry Brody, M.C.). The body is that of a well-developed white male, estimated weight 160 lbs. There are extensive subjunctival hemorrhages bilaterally. Between the mid and posterior axillary lines, above the crest of the ilium, there is a partly healed eschar. The crust has dropped off, the base is yellow and granular, the edges are sharp, the ulcer base is 1.5 mm. below the skin surface. The

skin immediately around the ulcer appears slightly indurated and hyperemic. Otherwise the external appearance of the body is not remarkable.

The liver edge is at the costal border. The spleen, though enlarged, is within the costal border. The thymus is small. There are about 50 cc. of clear fluid in each pleural cavity. The abdominal organs are normally disposed.

The heart: The pericardial cavity contains 15 cc. of fluid; pericardial surfaces are smooth. The right ventricle appears dilated, otherwise shows no abnormalities. The endocardium of the left atrium, immediately above the posterior leaflet of the mitral valve, appears wrinkled and somewhat orange yellow. The chordæ tendineæ of the mitral valve are thickened. Along the line of closure of the anterior leaflet there is a thickened fibrous ridge about 2 mm. in thickness and 1.5 cm. in length. The valve does not appear deformed and was undoubtedly functionally sufficient. In the left ventricle there are several patches of endocardial thickening, light yellow in appearance. The largest of these involves the base of the anterior papillary muscle. The thickened portion of the endocardium is light yellow. The left ventricle is neither dilated nor hypertrophied. The aortic valve shows nothing remarkable. The coronary ostia are normal. The coronary arteries show some atheromatous streaking, but no serious impairment of their lumen. The aorta is elastic with moderate atheromatous streaking.

In the lungs, old fibrous adhesions are found between the lobes bilaterally. Pleural surfaces are smooth and glistening, except for an area about 10 cm. in diameter on the lateral aspect of the right lower lobe, where it is a dull purple. The surface at this site has lost its sheen. The upper lobes bilaterally are partly crepitant, the lower lobes have a somewhat rubbery consistency. A number of tiny fibrous anthracotic nodules are scattered throughout both lungs. The lower lobes appear somewhat atelectatic. On palpation there are scattered small areas which feel firmer than elsewhere. The general surface on section is dull purple, and tiny areas perhaps slightly more gray and drier appear throughout. The larger bronchi contain blood streaked mucus. The pulmonary vessels are normal. The hilar lymph nodes are enlarged and soft. No calcific or caseous nodes are found.

The spleen is about 3 times normal size. The capsule is smooth, there is a spleniculus. On section, the pulp is firm and deep purple. The Malpighian bodies are very prominent and numerous, larger than normal. The splenic vessels are normal.

The kidneys appear slightly large, the capsule is tense but strips easily leaving smooth surfaces. The cortex appears very pale and light gray. The glomeruli can scarcely be made out. The outer 2 or 3 mm. of each pyramid is deeply engorged. This forms a symmetrical pattern throughout both kidneys. The central portion of each pyramid and the renal papillæ are unusually pale, somewhat glassy in appearance. This hyperemic scalloping, separating the cortex from the central portions of each pyramid, makes a striking picture. The renal pelves show subepithelial hemorrhages. The ureters are normal. The urinary bladder is collapsed, its epithelium pale. There are only a few cc. of urine in the bladder. The trigone is normal, prostate small. The seminal vesicles contain rather viscid brown fluid. The epididymes and testes are normal.

The liver is normal in size, capsule is smooth, architectural pattern preserved. There is no gross evidence of fatty change. The gall bladder is distended with viscid green bile, the duct system is normal. The pancreas is not remarkable. The gastrointestinal tract is normal except for slightly enlarged mesenteric glands.

The iliopsoas muscle on the right side is the seat of extensive hemorrhage. It is friable. No similar lesion is seen in any of the other muscles.

The brain was not removed.

Histologic Study (Capt. Herbert J. Levin, M.C.). The heart shows an arteriolitis and periarteriolitis with marked narrowing of the vessel lumina due to endothelial hyperplasia. There are numerous small areas of hemorrhage, principally perivascular and the myocardium shows profound cloudy swelling, fragmentation and hyaline necrosis. In some areas there is advanced fatty replacement. Another section shows massive subepicardial hemorrhage. In a section of a cardiac leaflet there is marked vascularized fibrous thickening but no evidence of recent inflammation. Sections of the aorta show advanced

vasculitis and perivasculitis of the vasa vasorum.

The lungs show numerous heart failure cells in the alveoli. The alveolar septa are thickened due to accumulations of small and large mononuclear cells. Few of the blood-vessels show initimal hyperplasia.

The spleen sections show pulp hyperplasia with considerable blood pigment present in the endothelial cells. The splenic corpuscles are atrophic. They show hyperplasia and hyalin necrosis of the germinal centers. Lymph node sections show only endothelial hyperplasia and anthracosis. The liver sections show marked vasculitis and perivasculitis of the interlobular vessels. There are prominent small cell aggregates in the periportal spaces. Old blood pigment is found in the periphery of the liver lobules. The pancreas shows chronic inflammatory cell infiltration and fibrosis of the interstitial connective tissue.

The kidney sections show a pronounced vasculitis and perivasculitis. Blood-vessels in the medulla are greatly dilated and packed with red cells. The proximal convoluted tubules are dilated, swollen and tufted; in their lumina is granular débris. There is a prominent lymphocytic invasion of the interstitial tissue and there are occasional delicate adhesions between the congested glomeruli and the Bowman capsules. The adrenals, testes and prostate present no pathologic changes.

Pathologic Diagnosis. 1. General: Tsutsugamushi disease (scrub typhus type), acute, severe.

2. Cardiovascular System: (*a*) Vasculitis and perivasculitis. (*b*) Hemorrhages multiple. (*c*) Myocardial cloudy swelling and hyaline necrosis. (*d*) Fatty changes. (*e*) Endocarditis, rheumatic, mitral, old, healed. (*f*) Pericardial effusion.

3. Respiratory System: (*a*) Vasculitis, minimal. (*b*) Interstitial pneumonitis. (*c*) Congestion. (*d*) Pleural adhesions, bilateral.

4. Spleen: Hyperplasia, marked.

5. Liver. Vasculitis and perivasculitis.

6. Kidneys: (*a*) Vasculitis and perivasculitis. (*b*) Interstial nephritis.

7. Pancreas: Interstitial pancreatitis.

8. Muscle: Hemorrhage, massive, iliopsoas, right.

9. Miscellaneous: (*a*) Hemorrhages, subconjunctival. (*b*) Ulcer, of skin, healing, right posterior lumbar region.

Epicrisis. Cause of death in this case was an uncomplicated typhus infection with most marked changes in the heart muscle.

Treatment. There is no specific treatment for scrub typhus fever. Good nursing care, absolute rest which includes the avoidance of measures which will disturb the patient, maintenance of nourishment, fluids, salt and vitamin intake form the backbone of any successful management. The treatment as recommended in War Department Technical Bulletin (Med. 31)[3] is based on a large accumulated experience with scrub typhus and is sound and well worth applying. One must be cautioned against the temptation to over-treat these patients; excessive symptomatic treatment should be discouraged.

Penicillin and the sulfonamides are without value unless secondary infection complicates. Indeed, sulfa drugs may prove harmful. The daily administration of 6 gm. of salt is important, a hypochloremia has been demonstrated in the fever stage. Salt may be given orally, or by slow intravenous drip as normal physiologic saline; 3000 cc. of fluid should be given per day, orally and parenterally. As long as intravenous infusions are given slowly, the circulatory system is unaffected. Digitalis is of no value except in acute congestive cardiac failure. Plasma is not needed unless hypoproteinemia with edema occur, which we did not experience in our patients. Some have utilized plasma as a measure to maintain blood pressure; we tried it but failed to note any effect. Oxygen therapy proved of little value in the pneumonia seen in the disease, but of more value in complicating congestive heart failure. 2500 to 3500 calories per day is a necessary factor for the patient; however, few are disposed to eat during the acute stage and must be constantly urged. The eschar requires no treatment other than a sterile, dry dressing; it heals spontaneously within a few weeks leaving a scar of no moment. The pneumonitis requires no special treatment other than a sedative for cough

now and then; the meningeal manifestations likewise require no special measures; both reverse to normal with recovery. This is also true of the hypotension. Cardiac failure requires prompt digitalization. The conjunctivitis may occasionally require a mild astringent, otherwise, even if severe, is best left alone. The deafness is temporary and should be handled only with reassurance.

The *convalescence*, once recovery stage is reached, assumes a most important rôle in restoration of the individual. Rest periods varying from 1 month in mild cases to 6 months in very severe infections may be required to counteract the prostration, asthenia, weight loss and reverse the pathology characteristic of this disease. Occasionally it becomes difficult to estimate when a soldier is fit to return to duty following this infection, as is illustrated by the 6 patients who required readmission for longer periods of rest. In all instances they were ultimately returned to full health and duty.

The attendant should never underestimate the value of reassurance in these patients. Anxiety states develop easily and erroneous ideas about the disease are current among them. Typhus fever is a dreaded infection among troops; since there are no "shots" to prevent it, they feel it is fatal; or if a victim should be fortunate enough to survive, that he will be left a cardiac invalid for the remainder of his life. Reassurance will go far to relieve such patients and prevent a disabling neurosis after recovery.

Study of a large series of convalescent typhus cases reported by the Chief Surgeon, United States Army Forces in the Far East[5] in which physical signs, roentgen findings, electrocardiograms, vital capacities and exercise tolerance tests were performed, demonstrated the absence of involvement of the cardiovascular system following recovery. Functional neurocirculatory symptoms were found tc be not more frequent than encountered in any other severe febrile state.

Without a specific curative treatment, the *prophylaxis* and prevention of the disease assume a very important rôle. There is no vaccine to date for general use which will actively immunize troops going into infected areas. The clearing of camp sites of scrub and grass, wearing full uniform to cover the body, frequent bathing, impregnation of clothing with repellents for mites (of which dimethyl phthallates are most effective, avoidance of sleeping on the ground) are all measures, which if possible to employ will reduce the rate to a minimum even in a heavily infected area. If the military situation permits the camp site or bivouac area to be carefully chosen away from scrub, grass, jungle or streams, much of the problem will be obviated. If military operations require bodies of troops in mite infested areas, rigid prophylactic discipline as recommended in War Department Technical Bulletin (Med. 31) will go far to wipe out the disease.

Discussion. Before the advent of World War II, scrub typhus fever or tsutsugamushi disease was a rare medical curiosity to the American physician. With the war and the transportation of large numbers of American troops to the Southwest Pacific and Far East theaters, the disease became a problem of paramount importance to the war effort, and to those of us engaged in caring for the health of these troops. For most of us, this was our first experience with scrub typhus fever. American texts offered only meager descriptions and discussions, and references upon the condition were not as numerous as one would like.

Following the war, it is more than likely that armies of occupation as well as civilians endeavoring to develop hitherto untouched resources in these lands will have to cope with the problem of scrub typhus. The large number of cases available for study among troops offers an excellent opportunity to accumulate more knowledge about the disease.

The etiology, transmission, clinical features, pathology and nature of scrub typhus are well established and under-

stood. The isolation of the rickettsia from the patient's blood stream and the Weil-Felix agglutination with OXK in titers of 1:160 or more are conclusive evidences of the disease. A negative agglutination, however, does not eliminate the diagnosis. The clinical features, namely the eschar, fever course, rash, adenopathy, splenomegaly, conjunctivitis, temporary deafness, with involvement of the brain, heart and lungs, are so characteristic that recognition of the disease, even in the absence of laboratory findings, is fairly simple. The need for laboratory confirmation assumes more importance in the doubtful cases.

In general, it may be said that all tropical diseases prevail because of inadequate sanitation. The incidence of these diseases is inversely proportional to the degree of sanitary measures employed. The American Army with its high sanitary standards has done a remarkable job in the midst of difficult war conditions, of reducing the occurrence and mortality of tropical diseases. Its methods and principles could serve as a basis for governmental projects after the war to eliminate the hazards of these infections wherever man may be obliged to go. The findings of the Surgeon General's investigating team in New Guinea, which our experience corroborated, have shown that scrub typhus can be reduced to a minimum even in heavily infected areas. After the war, it could be totally eliminated, if the knowledge we already possess is applied.

Until a specific vaccine is developed, or a better treatment devised to reduce the morbidity and mortality, the prophylaxis and employment of sanitary measures to prevent the disease offer the most hope for its eradication. These procedures have been so well laid down by the War Department, already referred to in this report, that their institution under the most rigid discipline is urged to keep the disease under control.

Summary and Conclusions. 1. Scrub typhus fever (Tsutsugamushi disease) as seen in a Station Hospital in north New Guinea during a combat period in which our troops were exposed to the disease, is reported.

2. In an analysis of 75 cases, 2 died, 73 recovered. The mortality of 2.7% is low for this serious infection.

3. The etiology, transmission, clinical features, laboratory findings, treatment and prevention are discussed.

4. The characteristic pathologic changes (a vasculitis and perivasculitis of the smaller vessels involving chiefly the heart, lungs, nervous system and reticulo-endothelial tissues) are well illustrated in the 2 autopsies presented.

5. With the knowledge at our disposal today, the institution of adequate sanitation and prevention measures, the disease could be eliminated in all areas where white man may travel after the war.

6. The record of the American Army in the reduction of the mortality and morbidity of this disease among our troops is to be commended.

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THE CLINICAL SIGNIFICANCE OF COLD HEMAGGLUTININS

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From the clinical standpoint, cold hemagglutins are considered important chiefly (1) because their appearance during the course of pulmonary infections may aid in the diagnosis of primary atypical pneumonia, and (2) because their development from whatever stimulus may be followed by vascular occlusion and rapid destruction of erythrocytes.

The literature pertaining to cold hemagglutinins have been reviewed recently by Stats and Wassermann.[42] It is, therefore, necessary only to point out that these agglutinins were thought to be of relatively little consequence until 1943 when Peterson, Ham and Finland[35] made the important discovery of their association with atypical pneumonia. The immunologic properties of cold agglutinins had been presented in detail by Clough and Richter[3] in 1918 and by Wheeler, Gallagher and Stuart[45] in 1939. In retrospect the 2 cases presented by these authors might well be labeled "primary atypical pneumonia." However, the relationship between the pneumonitis and the presence of these peculiar antibodies was not recognized at the time of their observations. Although numerous brief reports concerning cold agglutinins in atypical pneumonia have appeared since the early months of 1943, many questions remain incompletely answered. The investigations reported in this paper were, therefore, undertaken with the following objectives:

1. To study certain technical factors affecting the results of tests for the presence of cold hemagglutinins in human serum, and thereby to propose a suitable test for routine hospital use.

2. To study the development of cold hemagglutinins in primary atypical pneumonia with special reference to (*a*) the incidence of titers above the range commonly encountered in other diseases and in normal individuals, (*b*) the time of their appearance and disappearance, (*c*) the relationship between titer and severity of illness, and (*d*) their diagnostic value.

3. To determine the extent to which cold hemagglutinins develop in diseases other than atypical pneumonia, particularly in other respiratory infections and in diseases associated with splenomegaly.

4. To determine whether or not cold agglutinins found in association with various disorders have any distinctive immunologic properties which might aid in differential diagnosis.

5. To make special note of any hemolytic or vascular complications that might be attributed to the presence of cold hemagglutinins.

Methods. Blood was collected in sterile, corked tubes, and the serum was separated by centrifugation after the blood had stood at room temperature for several hours. Any specimens that had inadvertently been placed in the refrigerator were warmed in an incubator at 37° C. for 1 hr. before being placed in the centrifuge.

In the majority of instances the first tests of the sera were made within 1 wk. after the blood was drawn, and nearly always within 2 wks. For purposes of storage, all sera were kept in sterile Wassermann tubes tightly closed with rubber stoppers and sealed with paraffin. All tubes were stored at 4° C. in wire racks appropriately labeled and arranged for ready use. A card index file facilitated the cataloguing of specimens.

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Presumptive Tests. After a sufficient number of sera had accumulated, presumptive tests were carried out by placing 0.1 ml. of each specimen (without inactivation) in the bottom of a 10 x 75 mm. tube. To each tube 0.3 ml. of a 0.67% suspension of Group O human red blood cells in physiologic saline solution was added. The tubes were then shaken and placed in the refrigerator overnight at 4° C. The following morning the tubes were examined grossly for the presence or absence of agglutination. Those showing no clumping of the red cells were designated as negative and were not ordinarily retested; those showing ± agglutination were recorded as positive in a 1:4 dilution of serum and were likewise not ordinarily retested.

Titration of Serum. Sera giving stronger reactions were titrated as follows:

Result of presumptive test	*Range of dilutions set up in titration*
+	1:4 to 1:32
++	1:4 to 1:128
+++	1:4 to 1:256
++++	1:4 to 1:1024 (or higher)

Serial 2-fold dilutions of serum were made with saline in 10 x 75 mm. tubes. To 0.5 ml. of each dilution was added an equal volume of a 1% suspension of Group O human red cells. The tubes were then shaken, placed in a refrigerator at 4° C. overnight and examined grossly the following morning. The racks were removed from the refrigerator 1 at a time and if there was any delay in the examination, they were placed in a shallow pan of cracked ice in order to maintain the temperature as near 4° C. as possible.

Each tube was held in a nearly horizontal position and gently shaken (usually 3 to 5 times) until all cells in the bottom had been dislodged. The cell suspension was then carefully scrutinized over a well-illuminated white background and the last tube showing grossly detectable agglutination was taken as the end-point. Titers were recorded in terms of the *final* dilution of serum after addition of cell suspension. That is, the first tube containing 0.25 ml. serum + 0.25 ml. saline + 0.5 ml. cell suspension was regarded as having a 1:4 dilution. Reversibility of the agglutination was checked by examining the tubes after standing at room or incubator temperature for 1 or more hours.

Preparation of Cell Suspensions. Nearly all of the tests recorded in this paper were made with Group O red cells from 1 of 3 normal individuals. Approximately 5 ml. of blood were mixed with 1 ml. of 3.8% sodium citrate. The plasma was removed after centrifugation and the cells washed 3 times with saline, after which 0.67% suspensions in saline were prepared for presumptive tests and 1% suspensions for titrations. After mixing with serum, the final concentration of cells in each tube was 0.5%. Blood was not used after 24 hrs. and all cells were washed immediately before use. The variation in sensitivity of cells from different sources will be discussed later.

Investigation of Factors Affecting the Results of Tests for Cold Hemagglutinins. *Storage of Serum.* The rate at which demonstrable antibodies disappear from serum on storage is often an important consideration in serologic studies. The reports of Peterson, Ham and Finland,[35] and Horstmann and Tatlock[19] indicate that cold hemagglutinins are less apt to be present in high titer in sera stored 1 to 14 mos., and Favour[9] emphasizes the decrease in titer that may occur during the first 3 wks. of storage, especially if the serum is repeatedly warmed for sampling. McNeil,[31] on the other hand, found that titers were maintained during the first 6 weeks of storage but decreased markedly during the 2nd period of 6 weeks.

During the course of the present study 20 sera from 13 patients with atypical pneumonia were tested soon after collection (average interval 4 days) and again with identical technique after 2 to 10 mos. of storage at 4° C. without preservative. In each instance the suspension of red cells used in the second test was prepared either from the same donor used in the first test or from another donor whose cells had been shown to have approximately the same degree of sensitivity. Variations of 1 tube in either direction are considered insignificant. The results are shown in Table 1 and indicate that although considerable loss of potency may occur with storage, this is by no means the rule. Nevertheless it is clear that sera should be tested soon after collection if possible.

Use of Presumptive Test. The task of examining many sera at the same time can be greatly simplified by employing the

1-tube presumptive test already described. The final dilution of serum in the single tube of the presumptive test might be adjusted to 1:10 rather than 1:4, since titers less than 1:10 are of no significance. Use of the presumptive test was adopted after repeated examinations of many sera for cold hemagglutinins failed to disclose any prozone phenomena.

Table 1.—Changes in Titer of 20 Sera From 13 Patients With Atypical Pneumonia After 2 to 10 Months' Storage at 4° C

Number sera showing no significant change				Number sera showing significant decrease in titer			
Same	1 tube lower	1 tube higher	Total	2 tubes lower	3 tubes lower	4 tubes lower	Total
6	5	4	15	1	3	1	5
Average storage: 213 days				Average storage: 153 days			

There is no advantage in using the presumptive test if a single specimen of serum is to be examined.

Choice of Red Blood Cells. The studies of Landsteiner and Witt,[26] Kettel,[22,23,29] and Stats and Wasserman[42] indicate that there is considerable variation in the sensitivity of red blood cells from individuals representing the various blood groups and subgroups. Kettel obtained lowest titers with autologous cells and highest titers with other erythrocytes of the same blood group. Humphrey,[20] on the other hand, found autologous cells far more sensitive than Group O cells.

Tests for cold hemagglutinins are ordinarily carried out by using either autologous cells from the patient or Group O cells from a convenient donor. The need for determining the degree of variation in sensitivity of erythrocytes from these sources is obvious. With this objective in mind, the following experiments were undertaken.

Relative Sensitivity of Group O Cells From Various Sources. Ten sera from 9 patients were titrated with fresh cells from 5 different Group O donors, including A. R., the donor who furnished cells for about 45% of the tests reported in this paper. The 10 sera were selected to include a wide range of potency. The titrations were set up in the usual way and the degree of agglutination in each tube was recorded. The results obtained with 5 of the 10 representative sera, as shown in Table 2, indicate clearly that the cells from donor A. R. are more sensitive than the others. However, the greater sensitivity of these cells is apparent only in titrations of relatively weak sera. When more potent sera (M. W. and J. D.) were tested, differences in sensitivity of cells from various sources were not readily demonstrable.

Titration of the 10 sera with cells from the same 5 Group O donors was repeated after the cells had been stored (with plasma, under sterile conditions) in the refrigerator for 3 days. The reactions were slightly weaker with the 3 day old cells but again the greater sensitivity of A. R.'s cells was apparent in the test with weak sera.

In the second experiment of this type, 31 specimens of serum from 30 patients were titrated with cells from donors A. R. and W. V., the donors whose cells had previously shown greatest and least sensitivity respectively. These sera were selected because they had given relatively low titers in preliminary tests. Twenty-six of the specimens gave significantly stronger reactions and higher titers with A. R.'s cells, 1 showed equal potency with cells from the 2 donors, and 4 of the sera agglutinated W. V.'s cells more strongly than A. R.'s. Unfortunately these titrations could not be repeated, but nevertheless the greater sensitivity of A. R.'s cells was apparent in tests with most of the sera, particularly the weaker specimens.

Cells from donor R. J., who had provided blood for about 50% of the titrations recorded in this paper, became available for study on Aug. 28, 1944. Eight

sera from 8 patients were titrated with cells from R. J. and A. R. with nearly identical results. A. R.'s cells showed only slightly greater sensitivity. For practical purposes it can be said that the cells of R. J. and A. R., which were used in about 95% of the tests included in the clinical study, were of nearly equal sensitivity and were the most sensitive of all cells tested. Most of the remaining 5% of the tests were carried out with cells from donor R. S. (see Table 2). The sensitivity of these cells was intermediate between that of A. R. and W. V. Detailed presentation of the above results is omitted to conserve space.

pensions prepared from the blood of 28 different donors. The blood groups of these individuals were as follows:

OMNRh+	10 donors
OMRh+	5 "
OMNRh−	3 "
OMRh−	2 "
ONRh+	1 "
ONRh−	1 "
A_1MNRh+	2 "*
A_1MRh+	1 "
A_2MNRh+	1 "
BMRh+	1 "
A_1BNRh+	1 "
Total	28 donors

* Including patient.

The degree of agglutination in each tube was recorded, and it can be said that the

TABLE 2.—RESULTS OF TITRATION OF FIVE REPRESENTATIVE SERA WITH RED CELLS FROM 5 DIFFERENT GROUP O INDIVIDUALS

		Dilution of serum					
Serum	Cells	1:8	1:16	1:32	1:64	1:128	1:256
G. C.	W.V.	±	−	−	−		
	R.S.	+	±	−	−		
	A.R.	++	+±	+	±		
	J.T.	+	±	−	−		
	J.K.	+	±	−	−		
W. D.	W.V.	−	−				
	R.S.	−	−				
	A.R.	+	±				
	J.T.	±	−				
	J.K.	±	−				
J. K.	W.V.	+	−	−			
	R.S.	+	±	−			
	A.R.	+±	+	±			
	J.T.	+	±	−			
	J.K.	+	±	−			
M. W.	W.V.	..	+++	+++	++	+±	±
	R.S.	..	+++	+++	++	+	+
	A.R.	..	+++±	+++	++	+±	±
	J.T.	..	+++	+++	++	+	−
	J.K.	..	+++±	+++	++±	+	±
J. D.	W.V.	..	+++	++	+±	±	−
	R.S.	..	++	+±	+	±	−
	A.R.	..	++±	++	+	±	−
	J.T.	..	++	+	±	±	−
	J.K.	..	+++	++	+	±	−

The belief that potent sera may give the same results with all human cells was further supported by the following experiment:

Serial dilutions of the serum of patient M. S. were made in large volume, after which 0.5 ml. portions were distributed to small tubes. The serum was then titrated in the usual way with cell suspensions prepared from the blood of 28 different donors. The blood groups of these individuals were as follows:

results with all cells were nearly identical (titer 1:1280 to 1:1920). On the following day fresh cell suspensions were prepared from the citrated, refrigerated whole blood of the 28 donors, and again the results were nearly identical.

An eluate was prepared from this same serum by absorbing the cold hemagglutinins with Group O cells (donor R. J.)

at refrigerator temperature. The serum was then removed, the agglutinated mass of cells washed with ice-cold saline and the antibodies finally eluted into warm saline which was added to a volume equal to that of the serum removed. The eluate thus prepared was likewise tested twice (2 days apart) with the cells of the 28 donors. Again the results with all cells were nearly identical (titer 1:640 to 1:960). The reactions were slightly but significantly weaker with the 2 day old cells.

Relative Sensitivity of Group O and Autologous Cells. In most of the investigations of cold hemagglutinins thus far reported, tests have been made with Group O cells. The wisdom of using the same Group O donor for all tests has been recognized by several authors, but unfortunately the same human donor is rarely available to any laboratory for a long period of time. In routine studies it will therefore be more convenient to test each patient's serum with his own cells, which will always be obtainable.

Investigations carried out in this laboratory indicate that absolute values obtained with autologous cells are not often significantly different from those obtained with highly sensitive Group O cells. Presumptive tests of 30 sera were set up in duplicate, using autologous and Group O cells (donor A. R.). Nine sera gave negative results with both types of cells, 10 gave identical reactions ranging from ± to +++ with both types, 7 gave slightly stronger and 4 slightly weaker reactions with the Group O cells. The few titrations carried out in a similar manner showed that, in general, autologous cells are only slightly less sensitive than Group O cells from donors R. J., and A. R. slightly less sensitive than Group O cells from donors R. J. and A. R.

Optimal Concentration of Cells. The final concentration of red cells, after addition of cell suspension to diluted serum, ranges from 0.1 to 1% in the studies reported by other investigators. Use of the former concentration resulted in much higher titers than the latter in the experience of the Fort Bragg Commission.[4] Similar results were obtained in this laboratory but a final concentration of 0.5% was decided upon for routine use because of difficulty in *gross* detection of agglutination of the more dilute suspensions.

Freedman and Mirsky[12] reported tentatively that the longer cells were stored, the more readily were they agglutinated. On the contrary, the investigations of the Fort Bragg Commission[4] and the less extensive studies carried out in this laboratory showed conclusively that red cells become much less sensitive to cold hemagglutinins after 3 or more days of storage. This was true even when sterile, citrated whole blood was stored in the refrigerator and the cells washed immediately before use; deterioration was more marked if the cells were stored in saline suspension. No loss of reactivity could be detected after 24 hours of storage, and the loss was minimal after 2 days of refrigeration.

All titrations recorded in the present clinical study were carried out with cells stored for less than 24 hours.

Period of Refrigeration of Serum-Cell Mixtures. There is general agreement that it is best to examine the serum-cell mixtures after refrigeration overnight for 14 to 18 hours. During the present study many tubes were inspected for agglutination after 1, 2, 4 and 18 hours of refrigeration at 4° C. Agglutination was nearly always maximal at 18 hours and the advisability of overnight refrigeration was evident.

Method of Examining Tubes. The technique used in inspecting tubes for the presence or absence of agglutination has already been described. In a number of instances the end-point of the titration was determined microscopically by transferring a drop of cell suspension to a plain glass slide and examining it under low power. Titers determined in this way were usually 1 tube higher than those read grossly, but it was felt that micro-

scopic observations offer no advantage because there is apt to be some irregularity in the extent to which the drop is warmed while being examined on the slide. Use of a hand lens is recommended by some, but gross inspection of cold hemagglutination is simpler and is apparently adequate.

Recording of Serum Dilutions. In this study all titers are recorded in terms of the *final* dilution of serum after addition of the cell suspension. The same policy was followed by the Fort Bragg Commission. Other authors, as noted in Table 5, either record titers in terms of original serum dilutions or fail to state their policy in this respect. Since the volume of cell suspension added is often much less than the volume of diluted serum, it is difficult to calculate the final serum dilution in these reports. In dealing with agglutination reactions of this type, much might be gained if all investigators chose to mix equal volumes of diluted serum and cell suspension and to report all titers in terms of the final dilution of serum.

Results of Tests for Cold Hemagglutinins. *Survey of Hospitalized Patients and "Normal" Individuals.* During the period beginning July 1, 1943, and ending Nov. 30, 1944, blood was collected from all adult patients admitted to the Strong Memorial and Rochester Municipal Hospitals and subsequently thought to be suffering from primary atypical pneumonia. The first specimen was drawn as soon as this disease was suspected in a given patient, and subsequent specimens at intervals of 2 to 10 days thereafter during the period of hospitalization. In some instances it was possible to obtain additional samples of blood after the patients had been discharged from the hospital. The final diagnosis of atypical pneumonia was based upon the clinical picture as a whole,[7,31,46] apart from the results of the tests for cold hemagglutinins.

During the period beginning Nov. 15, 1943, and ending July 15, 1944, an additional effort was made to collect blood in a similar way from all adult patients hospitalized with any type of infectious disease. It was impossible to carry out this program in full, but nevertheless, sera were collected from over 400 patients representing a wide variety of infectious illnesses. In addition, a number of specimens were drawn from patients with certain non-infectious disorders, particularly those associated with splenomegaly. Patients with acute illnesses were included in the series only if they had donated at least 1 specimen between 12 and 30 days (in most cases 12 to 20 days) after the onset of their symptoms. If blood had not been drawn during this interval, the case was placed in the unclassified group, which was, therefore, a heterogeneous "waste-basket" collection of cases but did not include any cases of atypical pneumonia. Results of tests of sera from patients with chronic diseases were tabulated without regard for the date of onset of illness. Of the 130 normal individuals whose blood was tested for the presence of cold hemagglutinins, 122 were medical students and the remainder were hospital personnel.

Altogether 1762 specimens of serum were collected from 987 persons and approximately 2000 separate tests were made for the presence of cold hemagglutinins (not counting presumptive tests of sera subsequently titrated). Many of the sera were titrated more than once, and in such cases the highest titer obtained was the one recorded for purposes of the survey.

Cold Hemagglutinins in Atypical Pneumonia. Table 3 shows the distribution of maximal titers reached by the various individuals according to type of illness. It is immediately apparent that high titers are uncommon except in primary atypical pneumonia, while low titers are encountered in a variety of diseases as well as in supposedly normal persons. However, it must be emphasized that lower titers may be of importance provided a rise or fall, or preferably both, can be demonstrated in serial tests of sera drawn during the patient's illness and convalescence. The changes in titer of cold hem-

agglutinins in the sera of 9 patients with maximal titers of 1:32 or 1:64 are shown graphically in Figure 1. All of these patients presented the familiar picture of atypical pneumonia.

Similar changes in titer were observed in most of the *acute* respiratory infections, other than atypical pneumonia, in which maximal titers of 1:32 or more were reached. However, titers of 1:32 or above were produced in only 8.9% of these cases as compared with 80% in the group with atypical pneumonia (Table 4). Pneumococcal pneumonia, unclassified pneumonia, pulmonary tuberculosis, bronchitis, nasopharyngitis and influenza are

TABLE 3.—DISTRIBUTION OF MAXIMAL TITERS OF COLD HEMAGGLUTININS ACCORDING TO TYPE OF ILLNESS

Disease	Number of cases with maximal titer of												Total cases
	<4	4	8	16	32	64	128	256	512	1024	4096	16,384	
Primary atypical pneumonia	5	2	2	..	4	9	6	9	2	4	1	1	45
Pneumonia unclassified	36	13	2	3	3	2	..	1	..	..	..	..	60
Probable pneumococcal pneumonia	48	13	3	2	3	3	..	..	..	..	..	..	72
Pneumococcal pneumonia with bacteremia	9	4	1	2	2	..	1	..	..	..	..	..	19
Active pulmonary tuberculosis	24	4	1	1	3	2	..	..	..	..	..	..	35
Pulmonary infarction	8	2	..	..	..	..	..	..	..	..	..	..	10
Acute bronchitis	3	3	1	..	1	..	..	..	..	..	..	..	8
Chronic bronchitis	3	7	1	..	..	2	..	..	..	..	..	..	13
Bronchiectasis	1	3	..	..	..	..	..	1	..	..	..	..	5
Lung abscess	1	1	1	..	1	..	..	..	..	..	..	..	4
Acute nasopharyngitis	14	10	2	..	1	..	..	..	..	..	..	..	27
Influenza A (epidemic)	44	9	2	..	2	..	..	..	..	..	..	..	57
Acute catarrhal jaundice	3	2	1	..	..	..	1	..	..	..	..	..	7
Infectious mononucleosis	7	6	2	1	4	1	1	..	..	..	..	..	22
Rubella	1	1	..	1	3	3	2	..	..	..	..	..	11
Mumps without orchitis	1	..	..	..	..	..	..	..	..	..	..	..	1
Lymphocytic choriomeningitis	1	..	..	..	..	..	..	..	..	..	..	..	1
Herpes zoster	..	..	..	..	1	..	..	..	..	..	..	..	1
Poliomyelitis	..	8	1	..	..	..	..	..	..	..	..	..	9
Acute rheumatic fever	6	1	..	1	3	1	..	..	..	..	..	..	12
Endocarditis, Strep. viridans	2	1	..	1	..	..	..	..	..	..	..	..	4
Streptococcal (hemolytic) infections	8	5	1	1	1	1	..	..	..	..	..	..	17
Staphylococcal infections	..	1	1	..	1	..	..	..	..	..	..	..	3
Meningococcal infections	13	2	..	2	..	1	..	..	..	..	..	..	18
Gonococcal infections	3	..	..	..	..	..	..	..	..	..	..	..	3
Early syphilis	3	..	..	..	..	..	..	..	..	..	..	..	3
Bacillary dysentery (Sonne)	2	1	1	..	..	..	..	..	..	..	..	..	4
Malaria, P. vivax	1	1	..	..	..	..	..	..	..	..	..	..	2
Leukemia	8	3	..	..	..	..	..	..	..	..	..	..	11
Pernicious anemia	2	1	1	..	..	..	..	..	..	..	..	..	4
Sickle cell anemia	1	1	..	..	..	..	..	1	..	..	..	..	3
Congenital hemolytic jaundice	..	..	..	1	1	..	1	1	..	..	..	..	4
Acquired (atypical) hemolytic anemia	1	1	..	..	..	..	1	..	..	..	..	..	3
Congestive splenomegaly	..	1	1	..	..	..	..	..	..	..	..	..	2
Idiopathic thrombopenic purpura	1	1	2	..	..	..	1	..	..	..	..	..	5
Splenomegaly unclassified	..	2	..	2	..	1	..	..	..	..	..	..	5
Cirrhosis of liver	1	7	2	1	2	2	1	..	..	..	..	..	16
Unclassified diseases	236	58	17	14	2	4	..	..	..	..	..	..	331
"Normal" individuals	67	36	13	6	6	1	1	..	..	..	..	..	130
Total	564	211	59	39	44	33	16	13	2	4	1	1	987

TABLE 4.—INCIDENCE OF HIGH TITERS OF COLD HEMAGGLUTININS IN VARIOUS GROUPS

Group	Total No. cases	Total No. sera tested	Cases with maximal titer of 1:32 or higher		Cases with maximal titer of 1:128 or higher	
			No.	%	No.	%
Atypical pneumonia	45	154	36	80.0	23	51.1
Other respiratory infections	291	700	26	8.9	2	0.7
All other diseases	521	768	44	8.4	11	2.1
"Normal" individuals	130	140	8*	6.2	1*	0.7
Total	987	1762	114	11.5	37	3.7

* The "normal" individual with a titer of 1:128 had been hospitalized 3 months previously because of an attack of "acute bronchitis." The "normal" person whose serum gave a titer of 1:64 had had atypical pneumonia 23 months previously.

the diagnoses of the 291 patients making up the group of miscellaneous respiratory infections. Although some of the patients with other types of acute infectious disease (rubella, infectious mononucleosis, catarrhal jaundice, etc.) developed cold agglutinins in titers of 1:32 or more, these cases are not considered separately in Table 4 because they do not enter into the differential diagnosis of atypical pneumonia.

In the *chronic* diseases, particularly

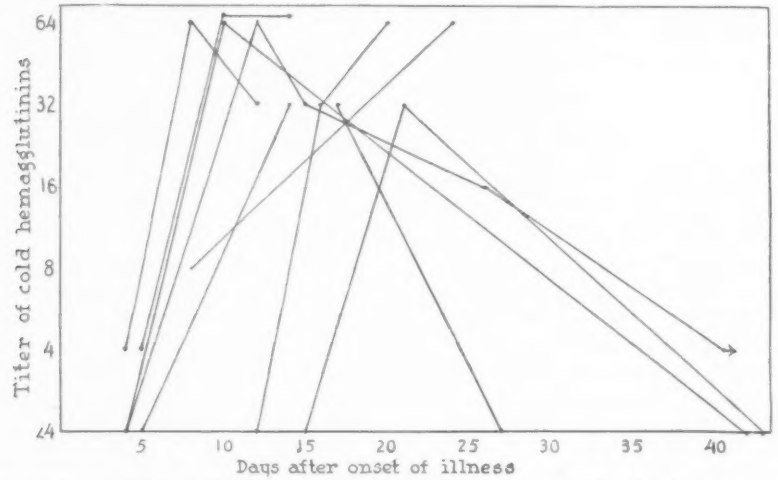

FIG. 1.—Rise and fall in titer of cold hemagglutinins in the sera of 9 patients with maximal titers of 1:32 or 1:64.

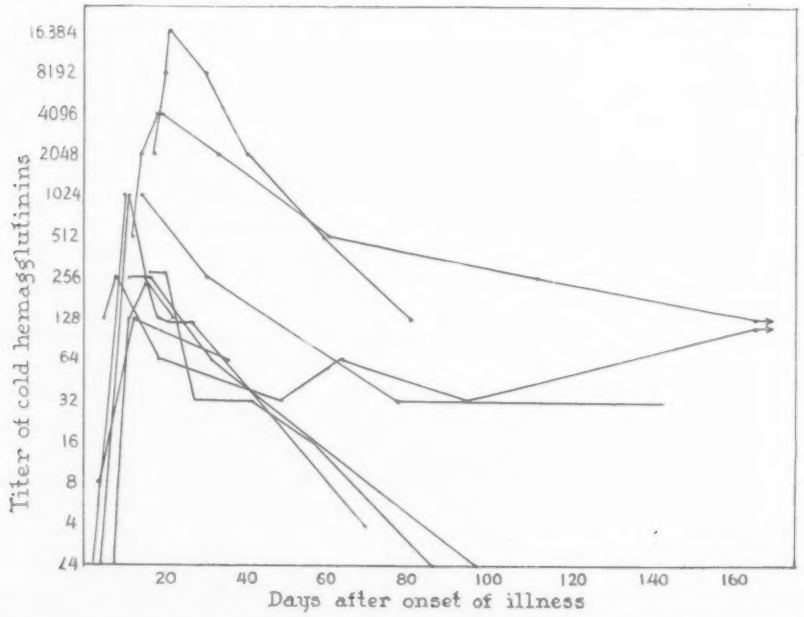

FIG. 2.—Rise and fall in titer of cold hemagglutinins in the sera of 10 patients with maximal titers of 1:128 or above. The specimen indicated by the upper arrow was drawn 7½ months after onset of illness; the lower arrow represents a specimen drawn at 10 months. The titer of both was 1:128.

those associated with splenomegaly, the titer of cold agglutinins remained relatively constant during the period of observation.

The rise and fall in titer of cold agglutinins in sera from 10 patients with maximal titers of 1:128 or above are plotted in Figure 2. It is apparent from Figures 1 and 2 that the titer of agglutinins usually rises most sharply during the 2nd week of illness and falls appreciably during the 4th week. This trend is also indicated in the hypothetical curve superimposed upon the dot graph of Figure 3.

However, it is significant that she had not been hospitalized since the original bout of atypical pneumonia.

Titers of 1:128 or above were observed prior to the 5th day of illness in only 2 patients (Fig. 3). In both cases, illness began insidiously and the recorded dates of onset cannot be considered reliable.

McNeil[31] found that titers were at their peak during the most serious stage of atypical pneumonia, which was 10 to 14 days after the onset of illness. At this time the fever was subsiding but pulmonary signs were most extensive and symp-

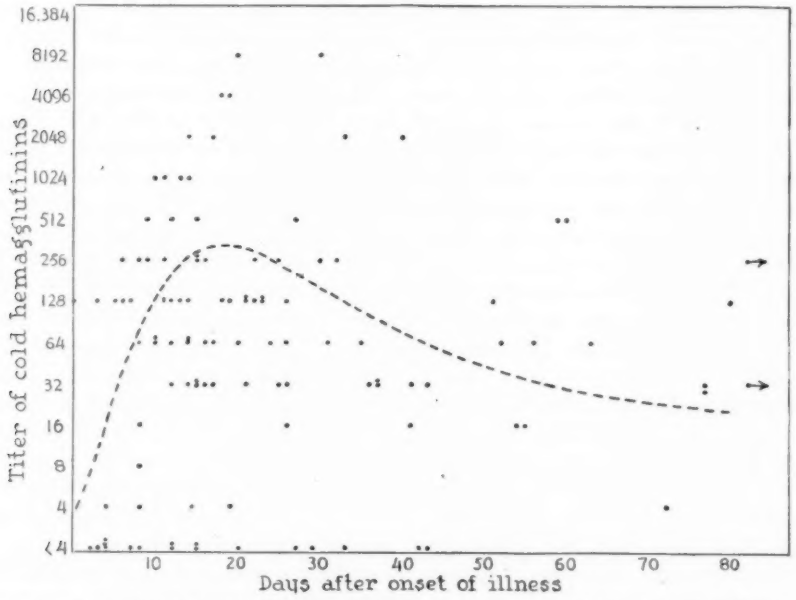

FIG. 3.—Titers of cold hemagglutinins in 115 sera drawn from 34 patients with primary atypical pneumonia at various intervals after onset of illness. The dotted hypothetical curve indicates the rise and fall in titer of a typical case during the period of illness and convalescence.

In several instances elevated titers persisted for periods of 4 to 10 months. The only patient who showed a significant rise in titer during this extended period of observation was a student nurse whose titer rose from 1:8 to 1:128 during the first 12 days of her illness. Three months later her titer had fallen to 1:32 but at 10 months had risen to 1:128. No information is available as to the occurrence of minor illnesses during this interval; however, it is significant that she had not been hospitalized since the original bout of atypical pneumonia.

toms most acute. During the present study this sequence of events was observed only in the more severe cases. In the milder cases signs and symptoms were often maximal at 4 to 8 days, and the peak of the cold agglutinin titer was not reached until 15 to 20 days after the onset of illness.

Although some observers[10,16,19,32] have found no correlation between the severity of the patient's illness and the height of

the titer of cold hemagglutinins, others[4,9,35] have reported at least a rough relationship. The Fort Bragg Commission[4] demonstrated a definite correlation between maximal titer and (1) number of days of fever above 100° F., and (2) extent of pulmonary involvement. In the present study, no such correlation could be shown. Some of the highest titers were recorded in relatively mild cases in which symptoms and signs were maximal 8 to 10 days before the peak of the agglutinin titer was reached.

Cold Hemagglutinins in Other Respiratory Infections. Unclassified pneumonias listed in Table 3 were those of uncertain etiology which did not follow the usual patterns of primary atypical pneumonia. Six out of 60 (10%) developed titers of 1:32 or above. One of these patients was a 71 year old woman who became ill rather suddenly and was found to have bronchopneumonia involving the left lower lobe. Three days after the onset of her illness, the white blood cell count was 22,500 per mm.,[3] the cold agglutinin titer was 1:4, blood culture was negative and culture of the sputum revealed a predominance of *Streptococcus viridans*. The response to sulfadiazine was equivocal. The headache and persistent cough of atypical pneumonia were lacking. The titer of cold agglutinins rose to 1:256 on the 13th day of illness—a rise sufficient to suggest that this patient's illness may have been caused by the same agent responsible for many cases of more "typical" primary atypical pneumonia.

The 6 cases of probable pneumococcal pneumonia which developed titers of 1:32 or above were caused by organisms of Types 2, 3, 7, 14 and 16 and the 3 bacteremic cases by Types 5, 6 (titer 1:128) and 8. The bacteremic cases which failed to develop agglutinins in titers above 1:16 were caused by pneumococci of Types 1, 3, 5, 7, 8, 12, 18, 22 and 25.

Sera from 35 cases of active pulmonary *tuberculosis* were tested at various intervals after the onset of symptoms. When serial specimens were obtainable from the same individual, no appreciable variation in titer could be demonstrated. However, most of these patients had probably been suffering from tuberculosis for 1 or more months before the first specimen was obtained. Three of the 35 patients had titers of 1:32 and 2 had titers of 1:64. In none of these 5 cases was there evidence suggesting concomitant infection with the agent of primary atypical pneumonia.

Siffert and Krautman,[39] Favour,[9] and Fetterman *et al.*[10] likewise found only low titers in a total of 106 tuberculous patients, and Bridge *et al.*[2] obtained completely negative results in a series of 45 cases. The latter authors, however, reported positive reactions (titer not stated) in 2 patients who were thought to have both atypical pneumonia and tuberculosis.

It can be concluded from these observations that the test for cold hemagglutinins is of some value in the differential diagnosis of tuberculosis and atypical pneumonia. Although a negative test has little significance, a positive result in high titer in a patient with pulmonary infiltration argues strongly for a diagnosis of atypical pneumonia. In such a case, however, the possibility of finding both diseases in the same patient cannot be entirely ignored.

The finding of a cold agglutinin titer of 1:256 in a patient with previously established *bronchiectasis* is of interest. This patient was acutely ill and febrile at the time of the test but there was no roentgenographic evidence of pneumonia. Unfortunately no conclusions can be drawn from this case because serial studies were impossible.

Grier[15] found that in two-thirds of 40 cases of bronchiectasis a mistaken diagnosis of primary atypical pneumonia was made initially and later corrected when the patients were discovered to have pneumonitis around a preëxisting bronchiectasis. However, it is reasonable to suspect that some of the acute exacerbations seen in patients with this chronic disease may be due to infection with the specific agent or agents of primary atypical pneumonia. Moreover, it is possible that some cases of bronchiectasis are initiated by

attacks of atypical pneumonia in which it is known that patients suffer from bronchiolitis, peribronchiolitis and intractable cough.

The failure of epidemic *influenza* (December 1943 and January 1944) to cause the development of cold agglutinins in 57 closely followed patients serves to emphasize once more that this disease is distinctly different from atypical pneumonia.

Little can be said about the finding of a titer of 1:128 in the serum of a single patient who was convalescing from *catarrhal jaundice.*

Six of 22 patients with *infectious mononucleosis* developed titers of 1:32 or above. The diagnosis in each case was established by the appearance of abnormal lymphocytes in the peripheral blood and sheep cell agglutinins which were readily absorbed by bovine cells but not by guinea pig kidney.[6] The development of cold agglutinins in infectious mononucleosis has been described previously by Belk,[1] McNeil,[31] Freedman and Mirsky,[12] and Spingarn *et al.*,[40] but the significance of these agglutinins in this disease is not yet clear.

The appearance of cold agglutinins in titers of 1:32 or above during the 2nd or 3rd week of illness in 8 out of 11 cases of *rubella* is surprising, and indicates that further serologic investigations of this disease should be made. In the present study* rubella ranks second only to atypical pneumonia as a cause for the development of cold hemagglutinins. Favour[9] reported a titer of 1:80 in a patient who had rubella 1 month after an attack of atypical pneumonia, but the titers found in 6 other cases were insignificant.

The occurrence of cold agglutinins in high titer in certain diseases associated with *splenomegaly* deserves special emphasis. A titer of 1:256 was repeatedly demonstrated over a period of 6 months in the serum of a patient with *sickle cell anemia* and a markedly enlarged spleen. Sera from 2 other patients suffering from the same disease but having no splenomegaly did not contain significant amounts of cold agglutinins.

Four cases of *congenital hemolytic jaundice were studied:* 1. Serum from 1 patient was drawn and tested at 8 and again at 20 months after splenectomy; the titers of these intervals were 1:4 and 1:16 respectively.

2. The second patient had all of the usual manifestations of the disease except splenomegaly. A single specimen was tested and showed a titer of 1:32. Splenectomy was not performed.

3. In the third case the titer was 1:256 prior to splenectomy and 1:128 and 1:4 at 8 and 40 days after operation respectively.

4. The titers in the fourth case were 1:128, 48 days and 2 days before splenectomy and again 12 days after operation.

The occurrence of cold agglutinins in *acquired hemolytic anemia* is discussed in a separate paper.[27] In only 1 of 3 cases included in the present study was there a titer of any significance. In this case complete recovery followed splenectomy and the blood picture returned to normal, but the cold hemagglutinins persisted in undiminished titer for at least 6 months. In 1 of 5 cases of *idiopathic thrombopenic purpura* with splenomegaly, the titer was 1:128 on the day before splenectomy and 1:16, 3 weeks later.

The recorded instances of the association of cold agglutinins with splenomegaly are sufficient to arouse speculation, but much more work must be done before the significance of this relationship can be stated. The disappearance of agglutinins after splenectomy in some cases and the persistence of the same in others[42] is puzzling. In this connection, it is of interest that Nakamura[33] found no change

* Ten of the 11 patients with rubella were Navy V–12 students from the College of Arts and Sciences of the University of Rochester. All became ill within a period of approximately 1 month. Lieutenant George Heckel, MC, USNR, very kindly assisted with the collection of serum from these patients and from many others in the same student body who were hospitalized because of various acute illnesses.

in the titer of cold hemagglutinins following splenectomy in normal rabbits.

The finding of cold agglutinins in some cases of *cirrhosis* of the liver is in accord with the experience of others.[42]

Cold Hemagglutinins in Normal Individuals. Positive results were obtained with the sera from 63, or nearly one-half of a group of 130 normal persons most of whom were medical students. However, titers of 1:32 or above were recorded in only 8 instances. The student whose serum gave a titer of 1:64 had had atypical pneumonia 23 months previously, and the student with a titer of 1:128 had been hospitalized 3 months earlier because of an attack of acute bronchitis.

Among the 58 students in the class that had suffered heavily during an institutional outbreak of atypical pneumonia 15 months previously,[46] there was a slightly *lower* incidence of positive tests and *lower* average titer than among the 64 members of another class who had entered school a year after the outbreak occurred. In the former group were 17 students who had had clinically apparent atypical pneumonia, yet none of these students had a titer greater than 1:8 after the 15 month interval.

The so-called "normal" individuals comprising the above control group were normal only in the sense that they were in good health at the time their sera were tested. This group had to suffice because persons with strictly negative past histories, with regard to respiratory infection, are practically unobtainable in this latitude.

It should be emphasized that a negative result with the technique employed in this study does not indicate complete lack of agglutinins. Many more positive results would be recorded if the test tubes were examined microscopically. In 1 unselected group of 200 sera, 70 of the specimens gave negative presumptive tests but agglutination was detected in 32, or nearly one-half, of these 70 tubes when the serum-cell mixtures were checked under the low power of the microscope. An even higher incidence of positive results could be obtained if the serum were separated from the clot at 37° C. and added to the cell suspension without any dilution.

Kettel's belief that cold hemagglutinins are present in *all* normal human sera (at least in minute amounts) is apparently well founded. He actually demonstrated these antibodies in 95% of 600 sera, most of which were collected from patients with chronic diseases.[22] It is clear that the reported absence of agglutinins in the sera of many individuals can be attributed entirely to the use of crude technique.

Other Serologic Tests of Sera Containing Cold Hemagglutinins. Complement fixation tests with psittacosis antigen were kindly performed by Dr. K. F. Meyer who reported essentially negative results from 42 sera. These specimens had been drawn from 15 different patients who had atypical pneumonia and developed cold agglutinins in titers ranging from 1:32 to 1:4096. Suggestive results were obtained in only 3 cases and in none of these was there any history of contact with birds.

Peterson, Ham and Finland[35] have reported similar findings, while Meiklejohn[32] and Levinson *et al.*[28] found little or no development of cold agglutinins in 4 patients shown to be infected with psittacosis-like viruses. These results serve to emphasize the fact that although psittacosis (or ornithosis) and primary atypical pneumonia of unknown etiology are clinically similar, they can be differentiated readily by serologic tests.

Sera containing cold agglutinins in high titer were tested with sheep cells at various temperatures. In addition most of the absorption studies reported by Clough and Richter,[3] and Wheeler, Gallagher and Stuart[45] were repeated with similar findings. The results of these investigations are described elsewhere.[48]

In addition an attempt was made to differentiate serologically the cold agglutinins found in patients with atypical pneumonia from those found in patients with hemolytic anemia, sickle cell ane-

mia, infectious mononucleosis and rubella. However, it was necessary to terminate this investigation before any positive results could be obtained.

Case Report. One of the most interesting cases encountered during the course of this study was that of a 23 year old white married woman who was thought at first to have lymphocytic choriomeningitis. She had begun to suffer severe headache 4 days before admission. Two days later she had fever and generalized aching and was given sulfadiazine without response.

On admission to the hospital Jan. 6, 1944, the temperature was 101.3° F., the neck was somewhat stiff, the throat was moderately injected and the lungs were clear. The white blood count was 9500 and the blood smear was normal. The spinal fluid contained 600 lymphocytes per c.mm. and 70 mg. protein per 100 ml. Cultures of the spinal fluid and blood were negative. A roentgenograph of the chest revealed increased density in the right cardiophrenic angle.

The patient improved rapidly and was discharged from the hospital 4 days after admission. On Jan. 10, 1944, the day that she returned to her home, sera collected on January 7 and 10 were tested and found to contain cold hemagglutinins in titers of 1:128 and 1:256 respectively. Additional specimens obtained on January 19 and February 12 yielded titers of 1:64 and 1:32 respectively. All of these sera were then tested for neutralizing antibodies against the virus of lymphocytic choriomeningitis with negative results.*

The patient's clinical history was checked thoroughly and it was found that she had had a dry cough for several days before admission and during her hospital stay, but said little about it to her attending physicians. After she returned to her home the cough became much more troublesome and productive. She was still coughing frequently when last questioned on Feb. 20, 1944.

It is unfortunate that attempts to isolate a virus from this patient were not made. Nevertheless, it seems likely, in retrospect, that the meningitis in this instance was caused by one of the agents currently responsible for many cases of atypical pneumonia. McNeil[31] mentions a case of lymphocytic choriomeningitis in which a cold agglutinin titer of 1:96 was found on the 8th day, but no details of this illness are given. Review of the literature reveals 9 cases of atypical pneumonia in which meningismus was a notable feature;[13,18,25,29,36] in only 2 of these[13,36] was the spinal fluid abnormal (lymphocytosis and elevated protein). The occurrence of encephalitis as a complication of atypical pneumonia is well established,[8,14,21,34] but there is obviously need for further investigation of meningitides found in association with pneumonitis.

Complications Attributed to the Presence of Cold Hemagglutinins. Peripheral vascular occlusion,[17,30,35,41] pulmonary infarction,[31,35] and hemolytic phenomena[5,19,35] have been observed by other investigators in patients whose serum contained cold agglutinins. As a rule, the agglutinins in these cases were found to have broad thermal amplitude and were often present in high titer.

With one exception, these complications were not observed during the present study in spite of the fact that 6 of the patients with atypical pneumonia developed titers of 1:1024 or above. Moreover, in 4 of these 6 cases, activity of the agglutinins at room temperature was readily demonstrable. The single exception was a patient with acquired hemolytic anemia whose course is described in detail elsewhere.[27,47] Although the agglutinins in this case were present in a titer of only 1:128, they were active at 37° C. and were associated with phlebothromboses and the rapid destruction of both autologous and transfused cells.

Discussion. *Technical.* The technique of testing for the presence of cold agglutinins as herein described has proven satisfactory for investigative purposes. However, the following technique is suggested for routine hospital use.

Collect 5 to 10 ml. of blood in a sterile tube. Separate serum from the clot after standing at room temperature 1 to 3 hours. Insert 8 or more small test-tubes in a rack

* The neutralization tests were carried out by Dr. Charles Armstrong, Chief, Division of Infectious Diseases, National Institute of Health, Bethesda, Md.

and place 0.8 ml. physiologic saline solution in the first tube and 0.5 ml. in the remaining tubes. To the first tube add 0.2 ml. serum (which need not be inactivated); mix thoroughly with a 1 ml. pipette, make serial two-fold dilutions (1:5, 1:10, 1:20, etc.) and discard 0.5 ml. diluted serum from the next to the last tube. The last tube contains only saline and serves as a control.

Prepare an estimated 1% suspension of the patient's own red blood cells by washing cells from the clot with 5 to 10 ml. physiologic saline solution and washing the cells 3 times with an approximately equal volume of saline. To each tube of diluted serum add 0.5 ml. of the 1% suspension of cells which will thus double the dilutions of serum originally made. Shake rack to mix cells and serum and place in refrigerator at 4° C. overnight.

Examine tubes immediately after their removal from the refrigerator by holding them in a nearly horizontal position over a well-illuminated white background. Shake each tube gently but quickly until all cells in the bottom have been dislodged. Record the titer in terms of the final dilution (1:10, 1:20, 1:40, etc.) of the serum in the last tube showing grossly detectable agglutination. After the tubes have been examined, place them in an incubator or water-bath at 37° C. for 1 hour to determine whether or not the agglutination is reversible.

Whenever possible the test should be made on the day the blood is drawn. If it cannot be done until a later date, the serum which has been separated from the clot on the 1st day should meanwhile be stored at 4° C. (or kept in the frozen state) under sterile conditions. The patient's clot, from which cells are to be washed, can be used after 3 to 5 days, if necessary, provided a small amount of serum is left in the tube and it is stored in the refrigerator under sterile conditions.

Clinical. There is considerable difference of opinion among the various observers as to the value of the test for cold hemagglutinins in the differential diagnosis of primary atypical pneumonia. Rich *et al.*[37] conclude that "the test, at present, has no value," and Freedman and Mirsky[12] obtained positive results in high titer as frequently with sera from patients with infectious mononucleosis as from patients with atypical pneumonia. On the other hand, Peterson, Ham and Finland,[35] Horstmann and Tatlock,[19] Shone and Pass-

TABLE 5.—INCIDENCE OF "SIGNIFICANT" TITERS OF COLD HEMAGGLUTININS IN REPORTED CASES OF ATYPICAL PNEUMONIA

Authors	Titer regarded as significant	Serum dilution recorded	No. cases studied	Cases with significant titers	
				No.	%
Horstmann and Tatlock[19]	1:4	Original	43*	27	63
Turner *et al.*[44]	1:32	Original	83	44	53
Shone and Passmore[38]	(Qualitative test only)		54	(54)	(100)
Meiklejohn[32]	1:40	Original	74	45	61
Fort Bragg Commission[4]	1:64	Final	93	29	31
Streeter, Farmer and Hayes[43]	1:40	Original	50	20	40
Fetterman, Moran and Hess[10]	1:32	Original	44†	29	64
Rich, Rae and McGoey[37]	1:64	Not stated	37	17	46
Freedman and Mirsky[12]	1:32‡	Original	35	10	29
Favour[9]	1:160	Original	46	18	39
Fowler[11]	1:20‡	Not stated	20	17	85
Humphrey[20]	1:4	Original	14	13	93
Present study	1:128	Final	45	23	51
Total	...	...	638	346	54

* The majority of the sera tested by Horstmann and Tatlock had been stored for 1 to 14 months.

† Heinztelman and Seligmann[16] reported separately 33 of the 44 cases reported by Fetterman *et al.*

‡ Titer selected by present author.

more,[38] and Humphrey[20] found cold agglutinins in nearly all cases of atypical pneumonia examined. Moreover Humphrey suggests that the test for cold agglutinins might even supplant roentgenographs of the chest in suspected cases of this disease.

The combined observations reported to date (Table 5) indicate that cold agglutinins appear in about one-half of all cases. This is only a very rough figure, however, because the denominator, that is, the total number of cases observed, cannot be reckoned accurately due to lack of clinical criteria for differentiation of atypical pneumonia from other respiratory infections. Moreover, it is likely that the syndrome known today as primary atypical pneumonia is produced by multiple agents, and perhaps only one of these is capable of stimulating the development of cold agglutinins. This suggestion is supported by the observations of McNeil[31] who found that these heterophil antibodies appeared in all of 15 patients with this disease during a fall epidemic, but in none of the cases observed by him during a winter period. During the present study no seasonal correlations could be made, and patients with and those without cold agglutinins presented essentially the same clinical features.

The test for cold hemagglutinins, like other agglutination reactions, is seldom helpful during the 1st week of illness, when accurate diagnosis is most difficult and most needed. By the 2nd week, when agglutinins appear, the diagnosis is often already established on the basis of clinical course and lack of response to sulfonamide therapy. Nevertheless, the confirmatory value of a positive test for cold agglutinins is apparent, especially in prolonged and "atypical" cases.

Final evaluation of this test cannot be made until more is known about the etiology of atypical pneumonia and about the mechanism by which these peculiar antibodies develop. In the meantime, however, it is urgent that whenever possible tests for cold hemagglutinins be carried out in all cases of pulmonary infection of uncertain etiology. It is particularly important that this be done in certain cases, such as those cited individually in this report.

Further studies of this type may aid materially in piecing together the varied clinical manifestations produced by one or more of the agents responsible for what is now called primary atypical pneumonia. Moreover, extensive use of this test during epidemics may be of great value in investigating the epidemiology of this increasingly important disease.

Summary. 1. Various factors affecting the results of tests for cold hemagglutinins were investigated and a test for routine use was proposed.

2. During a period of 17 months, 1762 specimens of serum were collected from 987 persons and examined for their content of cold hemagglutinins. Included in this study were 154 sera from 45 patients with primary atypical pneumonia; results with this group were as follows:

(*a*) Only 51% of these patients developed titers of 1:128 or higher which were above the range frequently encountered in other diseases and in normal individuals. Titers of 1:32 or above appeared in 80% of these cases and the *development* and *disappearance* of agglutinins in these lower titers was thought to be of added significance.

(*b*) Titers rose rapidly during the 2nd week of illness and fell during the 4th week but in some instances they remained elevated for 2 to 10 months. In severe cases the peak of the titer coincided with the period of maximal signs and symptoms (10 to 14 days) but in milder cases signs and symptoms were most pronounced at 4 to 8 days while the peak of the agglutinin titer was not reached until 15 to 20 days after the onset of illness.

(*c*) No relationship between titer and severity of illness could be demonstrated.

(*d*) The development of cold hemagglutinins during the 2nd week in a patient with pulmonary infection of unknown etiology appeared to be of distinct value in confirming the clinical impression of

primary atypical pneumonia. The value of the test for cold agglutinins in the diagnosis of certain "atypical" cases could not be estimated accurately because of lack of information concerning the etiology of these cases.

3. In 291 patients with respiratory infections other than atypical pneumonia and in 521 patients with a wide variety of other diseases, cold agglutinins were usually found only in low titer, except in rubella, infectious mononucleosis and in certain disorders associated with splenomegaly. Splenectomy had a variable effect upon the titer of agglutinins. Only 2 out of 130 "normal" individuals were found to have borderline titers, and in both instances a history of recent pulmonary infection was obtained.

4. A limited attempt to differentiate serologically the cold agglutinins found in patients with various disorders was unsuccessful.

5. Phlebothromboses and hemolytic phenomena were observed in association with the presence of cold agglutinins in a single case—a patient with acquired hemolytic anemia. None of the patients with atypical pneumonia developed complications that could be attributed to the presence of cold hemagglutinins, even though these antibodies were sometimes present in very high titer and were active at room temperature.

Conclusion. 1. A simple quantitative test for cold hemagglutinins is recommended for addition to the armamentarium of clinical laboratories.

2. Liberal use of this test can be expected to aid:

(*a*) In diagnosis of atypical pneumonia.

(*b*) In further defining the conditions under which cold hemagglutinins are produced.

(*c*) In explaining certain vascular and hemolytic disorders.

(*d*) In clarifying the nature of these peculiar antibodies.

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CLINICAL ARREST IN ENTEROCOCCAL ENDOCARDITIS*

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Endocarditis due to infection of the cardiac valves with *Streptococcus fecalis*, the enterococcus of Thiercelin, is well recognized by students who have given careful attention to the bacteriology of endocarditis, but this particular infection has been too much neglected in the clinical reports. Thus Lloyd-Jones,[2] in the Appendix to the monograph of Perry[3] on bacterial endocarditis, mentioned "*Str. fæcalis* or the enterococcus which occasionally produces endocarditis in man," while the principal author, in a table facing page 20, lists the microbic findings in 1000 well-authenticated cases of bacterial endocarditis in the literature from Harbitz (1899) to 1933 without any mention of the enterococcus. In general, this organism appears to have been called *S. viridans* without any attempt to differentiate within the viridans group. From our own experience we should estimate that about 10 to 15% of patients with bacterial endocarditis are infected with the enterococcus (*S. fæcalis*) as compared with about 60% infected with *S. salivarius*. The 2 species may be differentiated by behavior in cultures and by morphologic differences but of greater practical significance is the usual susceptibility of the salivarius strains to the bacteriostatic action of penicillin and their resistance to bacteriophages in contrast to the greater resistance of the fecalis strains to penicillin and their usual susceptibility to lysis by enterococcus bacteriophages. Bacterial endocarditis is all too often a wholly cryptogenic infection but sometimes it is possible to recognize antecedent disease of the intestine, of the uterus or more especially of the urinary tract in enterococcus endocarditis, while extraction of a tooth or other trauma to the mucous lining of the mouth, nose or pharynx is a more frequent antecedent in the infection of the heart valves by *S. salivarius*.

Recovery or arrest of the disease in patients with enterococcemia must be very rare. Ribeyro[4] has observed one such recovery in a patient who suffered from low-grade fever from Aug. 13, 1922, to Feb. 10, 1923, from whose blood the enterococcus was obtained by culture taken on January 17. This was not considered a case of endocarditis although the author was quite familiar with the association of enterococcus with bacterial endocarditis. Baehr[1] has shown 1 patient who apparently recovered from enterococcus endocarditis after treatment with large amounts of penicillin to maintain a blood level of 1.2 to 1.6 units of penicillin per ml. Apparently the last positive blood culture was observed some time in May 1944 in this patient.

We wish to present the summarized clinical chart together with brief discussion of 1 patient who has been observed for a considerable period and now appears to be in a state of arrest of this disease.

Case Report. P. M., male, aged 34, was born in New York City on Sept. 6, 1909, of Russian-Jewish parents. Evidently he was vigorous as a youth and played on the football team during high school years. In 1927 a heart murmur was discovered during a routine physical examination and he was sent to the cardiac clinic of the out-patient

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department of the New York Post-Graduate Hospital, where his first record is under date of Oct. 21, 1927. He then weighed 175¾ lbs. (70.7 kg.) and was 67 in. in height. He came to this clinic at intervals until Dec. 1, 1932. The record indicates chronic cardiovascular disease with aortic insufficiency of unknown etiology. He was not seen here again for nearly 11 years. On Feb. 15, 1943, he was again located and he reported to the clinic in response to a follow-up request. He had remained well during the entire intervening period, was now married and established in business and had been able to engage in strenuous activities. On March 8 he again appeared at the clinic, at which time there was an enlarged left ventricle, aortic insufficiency, regular sinus rhythm and electrocardiographic evidence of intraventricular conduction disturbance, myocardial damage and a suggestion of congenital heart disease, although a rheumatic etiology was regarded as worthy of consideration. The erythrocyte count was 6,230,000 and the sedimentation rate 11 mm. in 1 hr. He was dismissed with advice to return in 1 yr.

About Dec. 23, 1943, he suffered an attack of sharp pain in the right lower abdomen, accompanied by nausea and vomiting. On the next day the pain had shifted to the right upper lumbar region. After roentgenologic examination, his physician told him that he had no kidney stone and no appendicitis but there was a small amount of blood in the urine, discovered on microscopic examination. On or about Jan. 2, 1944, he first experienced pains localized in small areas, especially in the hands and feet. Some of these painful areas were marked by visible red spots under the skin, tender to pressure. His physician advised him to take his temperature every evening and he found an evening rectal temperature of 102° and normal temperature in the mornings. He was hospitalized near his home from Jan. 13 to 23. From Jan. 2 to 23 he lost 22½ lbs. (10.2 kg.) although his appetite has remained good.

On Jan. 23, 1944, he was transferred to the Post-Graduate Hospital. Physical examination on admission revealed enlargement of heart to the left; systolic blood

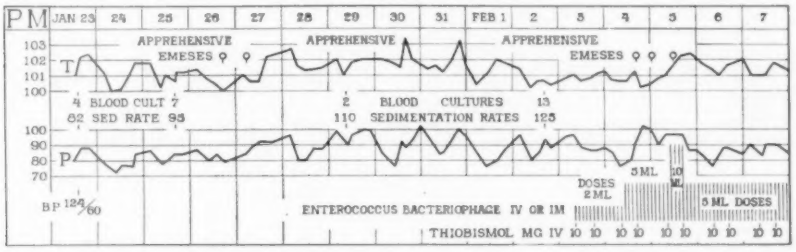

CHART 1

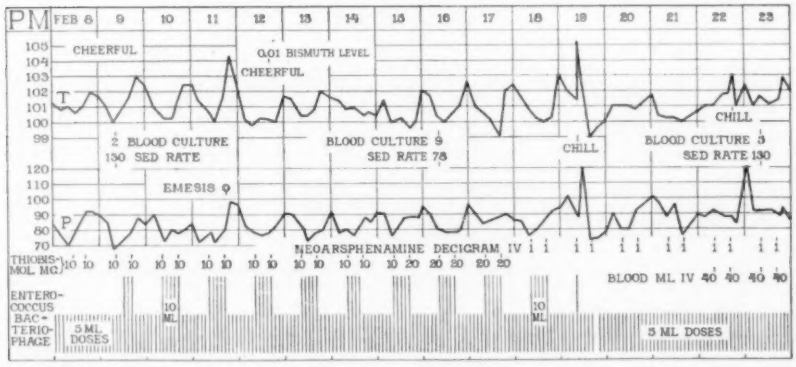

CHART 2

pressure 124 and diastolic 60; pulse rate 100; a blowing diastolic murmur best heard around the apical region. There was 1 small red spot on the plantar surface of the right great toe. Subsequent auscultation by several observers revealed a double aortic murmur best heard in the 3rd interspace at the left sternal border and the cardiac valvular alteration was considered to include a mitral

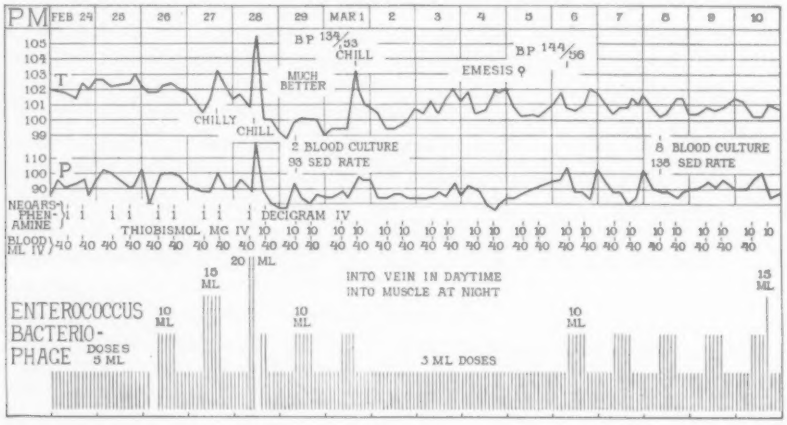

CHART 3

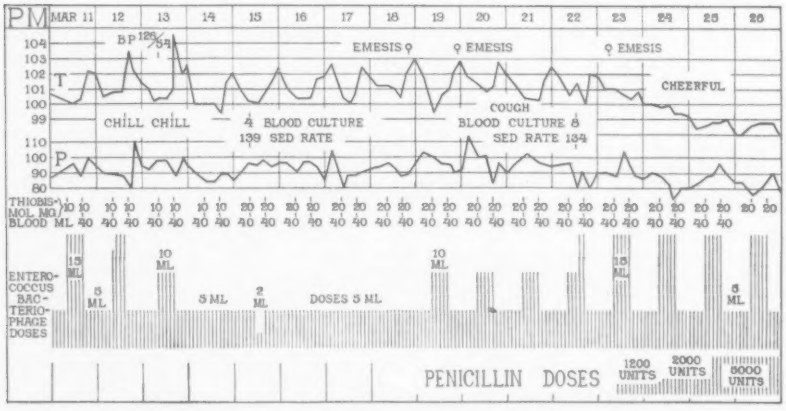

CHART 4

stenosis coupled with aortic stenosis and insufficiency. Blood culture taken on the day of admission was reported positive after 5 days and subsequent cultures of the blood taken on Jan. 25, 29, Feb. 2, 9, 16, 23, 29, March 8, 15 and 22 were consistently positive. The bacterial organism was a streptococcus causing greenish discoloration in the blood agar medium and fermenting carbohydrates in the manner ascribed to the enterococcus, *S. fecalis*. When tested in charcoal-adsorbed broth against various sulfonamides there was no evident inhibition of growth in concentrations of 30 mg. per 100 ml. of medium by sulfanilamide, sodium sulfathiazole, sodium sulfadiazine, sodium sulfapyridine or sodium sulfamerazine. Similar tests in neopeptone buffered broth showed complete inhibition of growth by neo-arsphenamine, 5 mg. in 100 ml. of medium, and slight inhibition by 0.5 mg. but none by 0.05 mg. per 100 ml. Mapharsen gave similar results. Thiobismol in a concentration of 100 mg. per 100 ml. of medium permitted, after 18 hours exposure, successful transplantation and slow growth in subculture; 1 mg. per 100 ml. of medium

completely inhibited growth in the test tube and 0.1 mg. gave slight inhibition, while 0.01 mg. per 100 ml. of medium exerted no perceptible inhibitory effect upon growth. Penicillin, 25 units per ml. of medium, did not kill the streptococcus but permitted successful transplantation after exposure for 18 hrs. at 37°. A concentration of 5 units per ml. inhibited growth in the test tube and a concentration of 0.625 unit per ml. exhibited slight inhibition as compared with the control broth. The same penicillin exhibited complete bacteriostatic effect upon a standard culture of staphylococcus (F.D.A. 209) in a dilution of 0.02 unit per ml. of medium. When these results were reported to the Committee in control of penicillin distribution, the permission, which had previously been granted to use penicillin to treat this patient, was immediately rescinded. The streptococcus was found to be susceptible to lysis by enterococcus bacteriophages and a specific bacteriophage active against this organism was prepared and available for use on Feb. 3. During this period of preliminary study from Jan. 23 to Feb. 3, the patient, his relatives and friends were very apprehensive and impatient with the inaction and delay and especially perturbed because penicillin was not being administered.

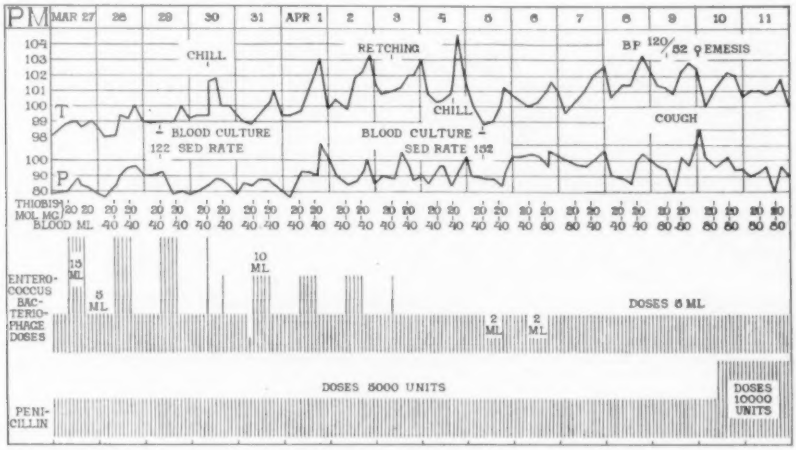

CHART 5

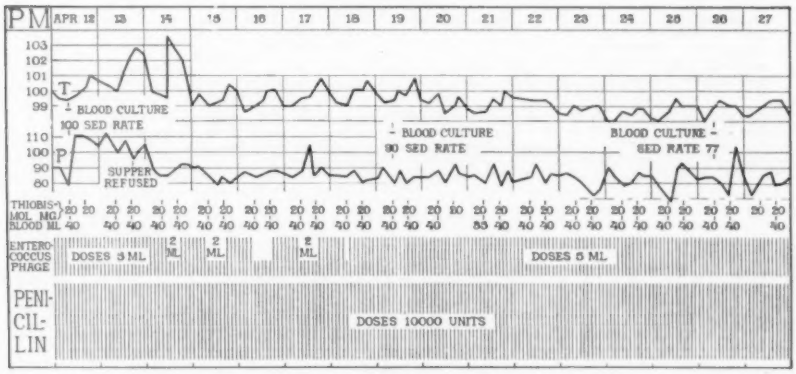

CHART 6

The hospital record is summarized in the charts, each covering a period of 16 days. The temperature reached 103.4° on Jan. 30 and 103.2° on Jan. 31, and the sedimentation rate was 125 mm. in an hour on Feb. 2.

Active treatment was started on Feb. 3 with intravenous injection of thiobismol (sodium bismuth thioglycollate), 10 mg., morning and evening, and specific enterococcus bacteriophage given every 2 hrs. by intravenous injection during the day and by intramuscular injection during the night. At first the phage dose was 2 ml., then 5 and on Feb. 5 it was increased to 10 ml. for some of the intravenous injections. It for the bismuth Feb. 18 to 28. Systematic use of small transfusions of citrated whole blood was initiated on Feb. 22 and continued with some interruptions throughout the period of hospital care.

Late in February the bacteriophage doses were increased to the limit of tolerance and there was a sharp reaction after 2 intravenous injections of 20 ml. on Feb. 28, characterized by chill, rise in temperature

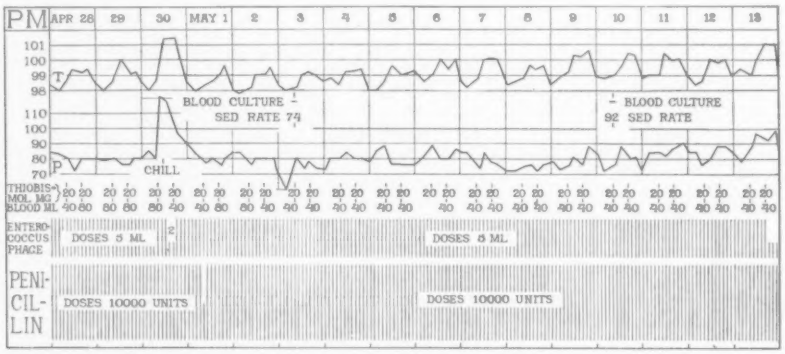

CHART 7

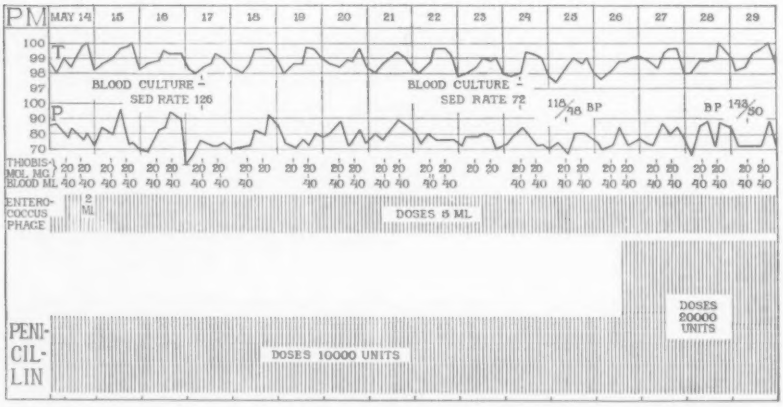

CHART 8

seemed that the larger doses of phage induced a rise in temperature and there was associated emesis on Feb. 11. The level of bismuth in the blood was approximately 0.01 mg. per 100 ml. on Feb. 12. On Feb. 19 the bacteriophage intravenous injection of 10 ml. at 8:20 A.M. was followed by a rather typical Hugh Young reaction. The usual dose given at 6:20 P.M. was omitted on this date. Neo-arsphenamine was substituted to 105.4°, subsequent rapid fall in temperature and a feeling of well-being on the part of the patient. The fever seemed somewhat ameliorated early in March but the results of blood culture and the sedimentation rate gave no excuse for optimism. Thiobismol replaced the neoarsphenamine on Feb. 28 and thereafter. The phage doses were again increased to induce reactions on March 12 and 13 and after a brief rest period the

larger doses were again administered from March 19 to April 2. The thiobismol was increased to 20 mg. twice a day on March 15 and continued at this level. On March 23 the left thumb was swollen and tender, apparently because of a rather deep embolic lesion; the patient was emotionally disturbed and vomited and he was very unhappy because he was not receiving penicillin. A experimental therapy. This calcium preparation was given in doses of 5000 units beginning at 12:15 NOON on March 25, by intravenous injection during the day and by intramuscular injection at night. As a rule, the penicillin contained in 1 ml. of sterile distilled water was mixed with the bacteriophage just before injection and this mixture ordinarily developed a slight cloudy floccula-

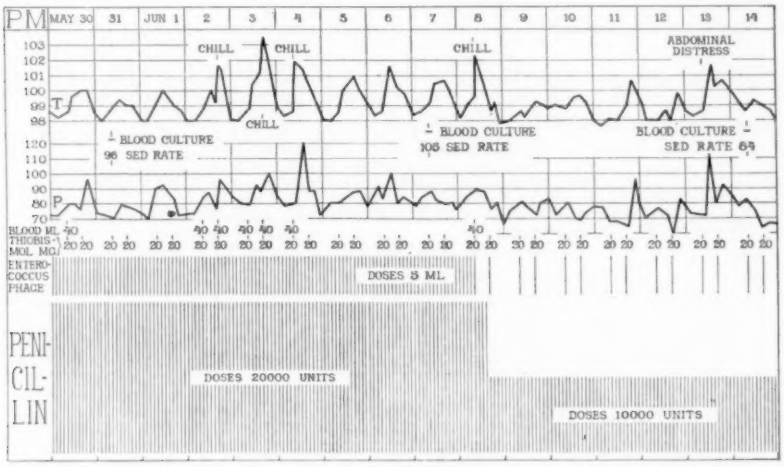

CHART 9

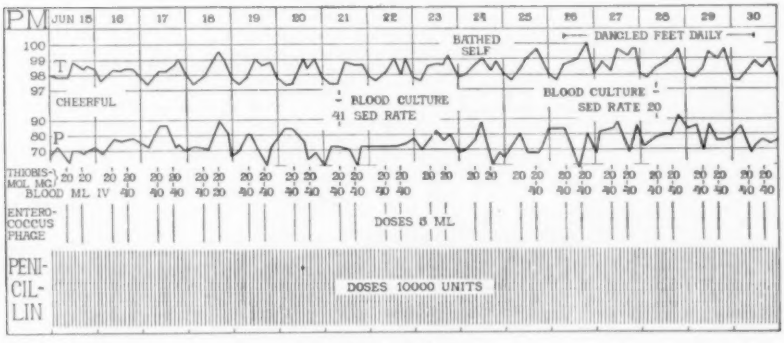

CHART 10

partially processed extract of the mold culture, in phosphate buffer solution, was administered by intramuscular injection in doses of approximately 1200 units ever 2 hrs., beginning at 2:15 P.M. March 23; this was stepped up to doses of 2000 units on March 24. We were then fortunate enough to obtain a supply of purified dry penicillin calcium which was apparently not acceptable for general use and therefore available for tion. The remarkable improvement in the temperature curve from March 23 to 29 would seem to have resulted from the addition of penicillin to the therapeutic program but the improvement was so prompt that a psychic influence might be considered. However, the first negative result of blood culture was observed in the specimen taken on March 29.

A test of the susceptibility of the invading

organism to penicillin had been made only from the early cultures recovered before bacteriophage therapy was instituted and no great change in the susceptibility was anticipated. However, studies of the streptococcus from the blood culture of March 22 revealed it to be morphologically and culturally similar to streptococci of the salivarius rather than the enterococcus group, resistant to bacteriophagic action *in vitro* and so susceptible to penicillin that an estimated 0.0049 Oxford unit completely prevented growth. The results of these studies, which were not available until April 9, may explain in part the very remarkable and totally unexpected response to penicillin therapy. The possibility of a second invader was considered, and though unlikely, cannot be disproved in this instance. The more acceptable theory is that the disease had been kept active by bacteriophage-resistant, penicillin-susceptible mutation forms of the original enterococcus after the bacteriophage-susceptible fraction had been overcome.

On March 26 there was a tender spot over the left 9th rib in the nipple line but no visible lesion. The spleen was not palpable. On March 29 there was a distinct embolic hemorrhagic spot in the ball of the right great toe, which was painful. A new lot of specific bacteriophage was brought into use on March 31 and this seemed to be more potent than the preceding preparation. The phage doses were maintained at 5 ml. or less for a long time after April 3. In spite of the continued small transfusions the patient remained moderately anemic and his sedimentation rate continued to be unsatisfactory. On April 10 the dose of penicillin calcium was increased to 10,000 units every 2 hrs. and maintained at this level until May 26. During this time the general condition seemed to be improving, the blood cultures remained negative and the temperature tended to remain below 100° F. Nevertheless the sedimentation rate continued to be unsatisfactory. The dose of penicillin calcium was increased to 20,000 units every 2 hrs.

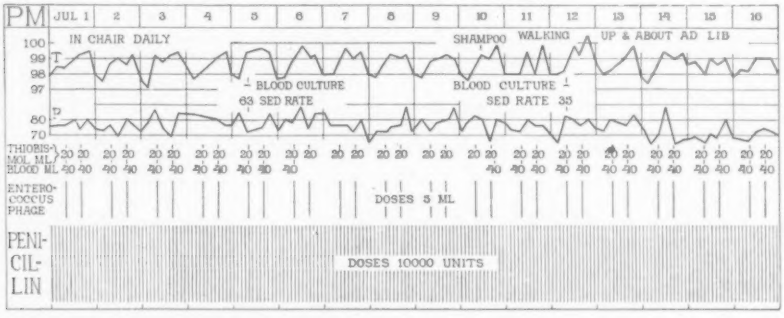

CHART 11

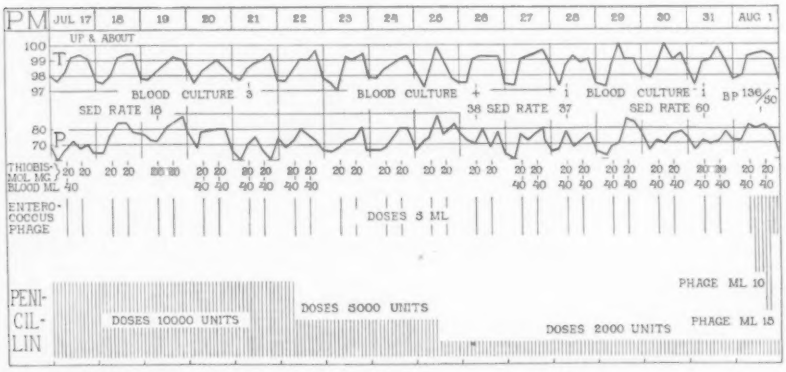

CHART 12

on May 26 and continued at this level until June 8.

During the first part of June there were several disturbances of temperature and some actual chills without other untoward manifestations. The small transfusions were omitted for a time but still there remained some elevation of temperature. On June 8

The clinical record from July 1 to 31 was regarded as satisfactory and the 2 daily doses of phage were continued while the penicillin was reduced to 5000 units every 2 hours on July 22 and further reduced to 2000 units every 2 hours on July 25. The blood culture taken on July 21 developed positive growth representing 3 organisms

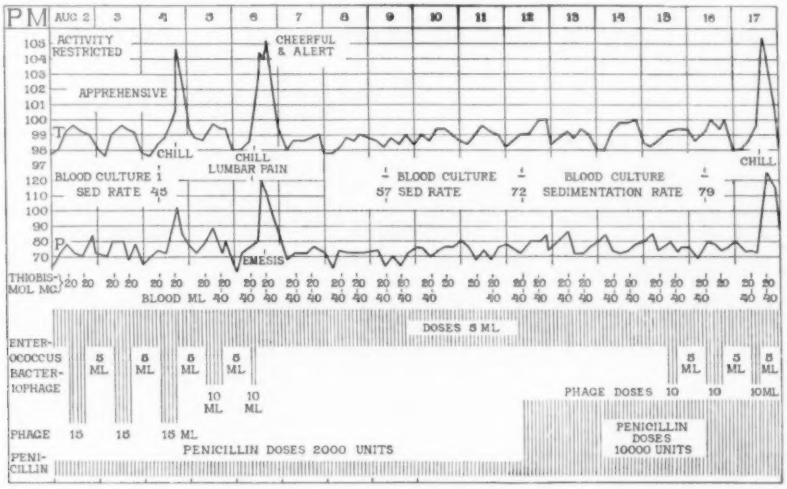

CHART 13

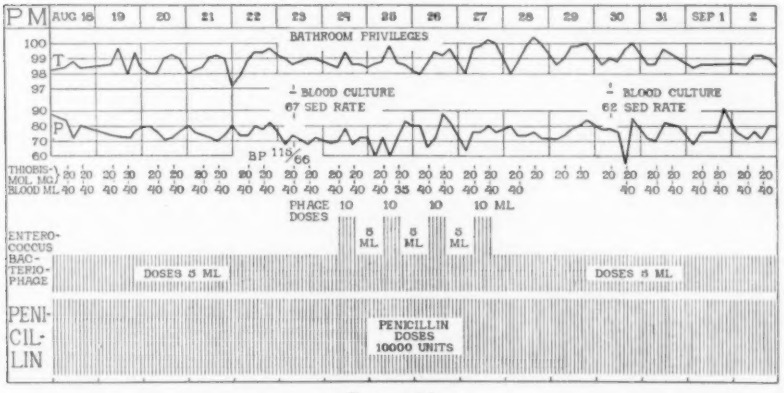

CHART 14

the bacteriophage doses were decreased to 5 ml. only twice a day and the penicillin was reduced to 10,000 units every 2 hrs. The record after June 14 suggests that the previous treatment may have been too drastic. Even the sedimentation rate came down on June 28. Greater activity was permitted and the patient seemed to be convalescent.

per ml. of the patient's blood, but this finding was not accepted as valid in the face of the other evidence of clinical improvement. However the bacteria, assumed to represent accidental contaminants, were subjected to searching study in the laboratory and by August 1 it became certain that they were of the same types as the streptococci of the many earlier blood cultures of this patient

taken in January, February and March. Meanwhile other specimens of blood taken on July 26 and 28 had given positive cultures and we were compelled to recognize that bacterial invasion of the blood stream had recurred. Subsequent blood cultures taken on July 31 and August 4 served to confirm this decision. The detailed bacteriologic studies of these cultures will be presented elsewhere.[2]

On August 1 the doses of bacteriophage were again scheduled at intervals of 2 hrs. day and night and some larger individual doses were given. Whereas the total daily amount had previously been 10 ml. from June 8 to July 31, the total daily amount on August 2, 3 and 4 was 110 ml., representing an 11-fold increase. These doses were somewhat diminished after the reaction on August 4 and again on August 6. The blood specimens taken on August 9 and 12 gave negative cultures, although the doses of penicillin had been kept at the former level of 2000 units every 2 hrs. It might, perhaps, have been an interesting experiment to have discontinued the penicillin altogether at this time, but we felt that this agent was having some bacteriostatic effect and its omission could not be justified. The dose was therefore increased to 10,000 units every 2 hours on August 12. The activity of the patient had been restricted

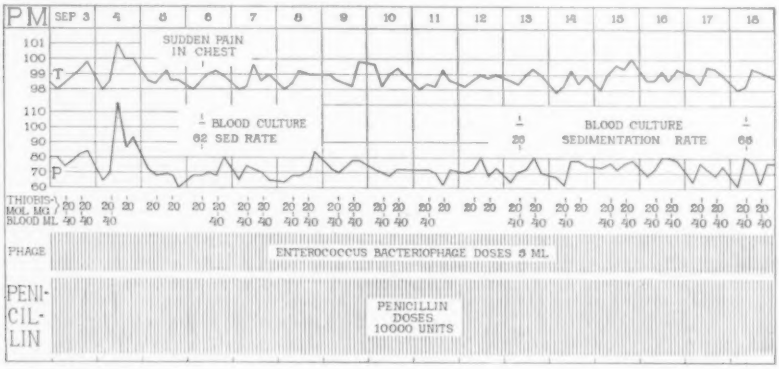

CHART 15

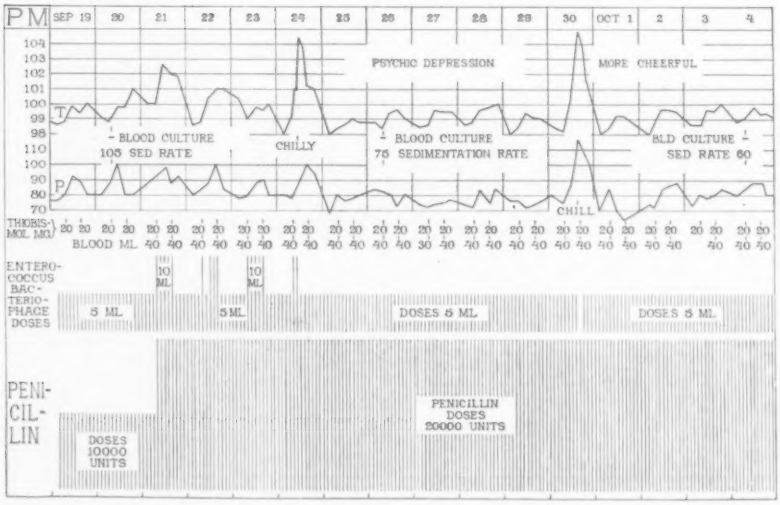

CHART 16

again on August 2 but he was again granted bathroom privileges on August 23.

The record from September 3 to 20 was fairly satisfactory. The patient was eating well and gaining in weight and strength. There were untoward incidents, however, such as that on September 4. On September 20 the patient complained of precordial discomfort and irritation of his eyes but he was willing to admit that it might be that he was just uneasy and apprehensive and wanted to be reassured about his progress. However, his sedimentation rate was 105 mm. in 1 hr. on this day. Therefore, on September 21 the penicillin was again increased to 20,000 units every 2 hrs. and the bacteriophage doses were also stepped up. The reaction on September 24 persuaded us to reduce the phage dose again and on September 30 one dose, that due at 4 15 P.M., was omitted. At the beginning of October the patient became more cheerful and optimistic.

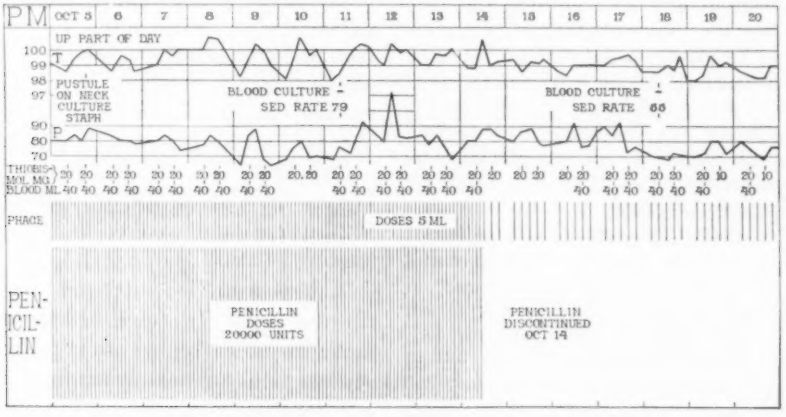

CHART 17

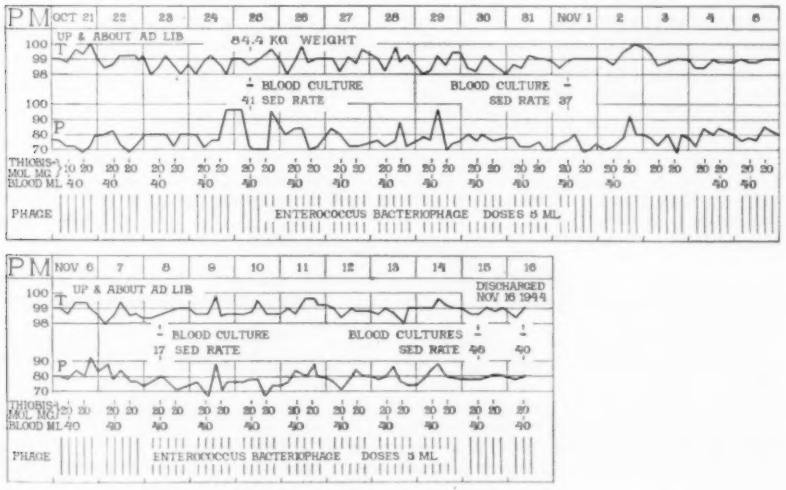

CHART 18

A small furuncle which appeared on the neck, October 5, yielded a culture of staphylococcus. This lesion was needled with staphylococcus bacteriophage and healed promptly. Its origin during the period of high penicillin dosage was a matter of interest. The patient was now very well nour-

ished, weighing 180 lbs. (81.6 kg.) and his general condition was so satisfactory that the penicillin was discontinued on October 14 and the doses of enterococcus phage cut to 4 in the period of 24 hrs., thus permitting a period of uninterrupted rest at night. The sedimentation rate still remained unsatisfactory. There seemed to be inadequate reason to prolong further his period of hospitalization and he was discharged on November 16. Since that time he has reported in person 3 times a week and on each occasion has received an intravenous injection of 5 ml. of his specific enterococcus bacteriophage. On November 29 he weighed 201 lbs. (91.2 kg.). A reducing diet has now been prescribed. On March 7, 1945, his condition was excellent.

Dec. 6, 1945. This patient has remained free from recurrent activity of his bacterial endocarditis and is actively engaged in business and in good condition when shown before a gathering of physicians on this date. Cultures of the blood, taken on 23 occasions since December 1944, have given negative result. The sedimentation rate has varied from 5 mm. in an hour on Aug. 30, 1945 to 78 mm. in an hour on Oct. 3, 1945, following an acute respiratory infection. A persistence of rheumatic disease is suspected and the patient is still reporting for examination at frequent intervals. On Dec. 6, 1945 the sedimentation rate was 30 mm. in 1 hour.

This is 1 of the 10 patients with bacterial endocarditis discharged from the hospital in a state of apparent arrest during 1 year. He is the only one in whom the infecting organism was the enterococcus. If he behaves in a manner like the other 9, there is good reason to hope that this state of apparent arrest may prove to be genuine and enduring. Other patients with enterococcus in the blood stream have more recently come under our care and it is hoped that more information may, in due course, be acquired in regard to this rather malignant malady.

Summary. 1. A man, aged 34, with known valvular disease of the heart since 1927, developed bacterial endocarditis late in 1943.

2. Repeated blood cultures were positive for *S. fecalis* and this organism was found to be rather resistant to bacteriostatic action of neoarsphenamine, mapharsen, thiobismol and penicillin; very resistant to the sulfonamides and quite susceptible to enterococcus bacteriophage.

3. After a long course of treatment in which several of these anti-infectious agents were used, the disease appears to have been arrested.

The partially processed penicillin was generously supplied by Rare Chemicals, Inc., Flemington, N. J., and the calcium salt of penicillin to a total of approximately 26 million units by Chas. Pfizer, Inc., Brooklyn, N. Y., for which we wish to make grateful acknowledgement.

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THE USE OF A "MODIFIED GLOBIN" FROM HUMAN ERYTHROCYTES IN HYPOPROTEINEMIAS*

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The importance of maintaining in patients a proper amount of circulating protein need not be emphasized at this time.[1] This problem is of particular importance in the preparation of patients for a surgical operation. In such patients, if a proper protein level is not maintained, certain complications may arise. Some of these complications, such as wound disruption, intestinal edema leading to obstruction, greater tendency to traumatic shock, have been sufficiently emphasized.[2] Others, however, such as edema of the lungs, susceptibility of liver to damage from infections, anesthesia,[9] etc., have not received sufficient attention.

It is not the purpose of this paper to discuss such complications, but to outline briefly basic principles for the selection of proper means to correct hypoproteinemia and to present evidence showing that modified human globin[3] may be advantageously used in many patients.

The use of globin in the treatment of hypoproteinemias is primarily suggested by the fact that plasma is not usually available in the quantity needed for the proper treatment of this type of patient. The utilization of discarded red cells for the production of globin would practically quadruple the available amount of protein for parenteral feeding from the same number of donations.

By hypoproteinemia is meant here a status brought on by: (*a*) insufficient intake of proteins over a sufficiently long period of time; (*b*) excessive losses, or (*c*) improper production. This status is generally revealed by a diminished total circulating protein, and frequently by diminished concentration of plasma protein. It is presumably accompanied by lowered protein reserves. The clinical manifestations of hypoproteinemia are generally minimal and present only in the severest cases or under special conditions such as operative procedure, injudicious administration of crystalloids, etc. The cases of latent or clinically silent hypoproteinemias form a very important group, the detection of which is essential. For this purpose an accurate history of the patient's eating habits is very important.

The nitrogen balance studies alone do not offer a criterion to judge the status of hypoproteinemia, nor are they sufficient for evaluation of the adequacy of treatment. Along with other criteria, they are of great usefulness. Amongst these criteria, the determination of the total circulating protein is probably the most informative. The total circulating protein in our work has been calculated from the plasma protein concentration, determined by the Biuret method,[4] and the total plasma volume determined by the T-1824 dye method.[5]

When considering the choice of means

* This paper is the 18th of a series on plasma and plasma substitutes from the Laboratory of Clinical Pathology of the Bryn Mawr Hospital. The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Bryn Mawr Hospital.

to correct hypoproteinemias, the following essential elements must be considered: (1) the severity of the hypoproteinemia; (2) the time that can be reasonably allowed for its correction; (3) the patient's general condition, with particular emphasis on the condition of the liver, kidneys and of the gastro-intestinal tract.

The patient with a mild to moderately severe hypoproteinemia but with unimpaired liver, kidney, and intestinal function offers no problem, unless the time element is very pressing. The oral route is alone satisfactory for these patients.

We are particularly concerned in this paper with the patient who has a severe hypoproteinemia, who is in a poor general state of health, and who must be prepared for an operation within as short a period of time as possible. A similar group is made up of patients who cannot be adequately fed by mouth, or who have impaired liver and/or kidney functions. These patients offer a difficult problem and require skillful handling. A classic example is the patient who is admitted to a hospital with intestinal obstruction, which has developed over a long period of time, causing progressive impairment of the nutrition, with lowering of the total circulating plasma proteins and presumably of the protein reserves. In this group of patients the oral route alone is generally inadequate to restore a proper plasma protein level and it is necessary to resort to parenteral feeding.

Human plasma and amino acid solutions prepared by digestion or hydrolysis of proteins are the only practical sources of nitrogen so far used intravenously. Modified human globin has been successfully used as a substitute for plasma in such patients. Some of the cases thus treated will be presented here.

Case Abstracts. Case 1. M. Mc., a white male, aged 78, suffering from portal cirrhosis with ascites received a total of 2490 cc. of modified globin containing 79 gm. of protein over 10 days while on a standardized diet with low fat and high carbohydrate and protein intake. The total circulating proteins rose from 166 gm. to 198 gm. during this period of time and the ascites decreased considerably, with a weight loss of 3.6 kg.

Case 2. H. H., a colored male, aged 44, was admitted to the hospital Sept. 26, 1944 suffering from a duodenal ulcer with gastric retention. The patient was given nothing by mouth for 5 days, water, salt, glucose and vitamins being administered intravenously. After this period he was placed on a liquid diet with 14 hourly feedings, which were gradually increased to consist of what follows: 10 feedings of 90 cc. of milk with 30 cc. of cream; 4 feedings of 120 cc. of strained fruit juice with a total N intake of only 4 gm. daily. This régime was maintained for 11 days (Oct. 1 to Oct. 11), during which time the urinary output was fairly constant, and the patient was in a negative N balance (Fig. 1). From Oct. 12 to Oct. 17 inclusive, the patient, in addition to the diet mentioned above, received daily intravenously 600 cc. of globin solution containing a total of 3.2 gm. of N. During this period of time the patient's measured total circulating protein remained constant at a figure near the calculated normal, and generally maintained a slightly positive N balance. Upon withdrawal of the globin, the patient returned to a negative N balance.

This patient was operated upon on Oct. 20 and a subtotal gastrectomy was performed. On the 21st postoperative day, the patient was placed on a diet with a total caloric value of 2500 calories daily and a total N intake of 9.6 gm. With this diet the patient was in a slightly positive N balance (Fig. 2). For a period of 3 days, from Nov. 24 to Nov. 26 inclusive, globin solution with a total nitrogen content of 3.2 gm. was administered daily. During this period of time definitely more N was retained than on oral feeding alone.

Case 3. J. B., a 52 year old white male, was admitted to the hospital Nov. 15, 1944 suffering from an inter-trochanteric fracture of the right femur. He appeared to be in a normal state of nutrition and was placed on a standard soft house diet with approximately 60 gm. of protein a day. This inadequate diet was maintained for approximately 2 months, at which time the patient became afebrile. He was then placed on a weighed diet consisting of: protein, 30 gm.; fats, 100 gm., carbohydrates, 295 gm. The total caloric intake was 2200 calories, and the

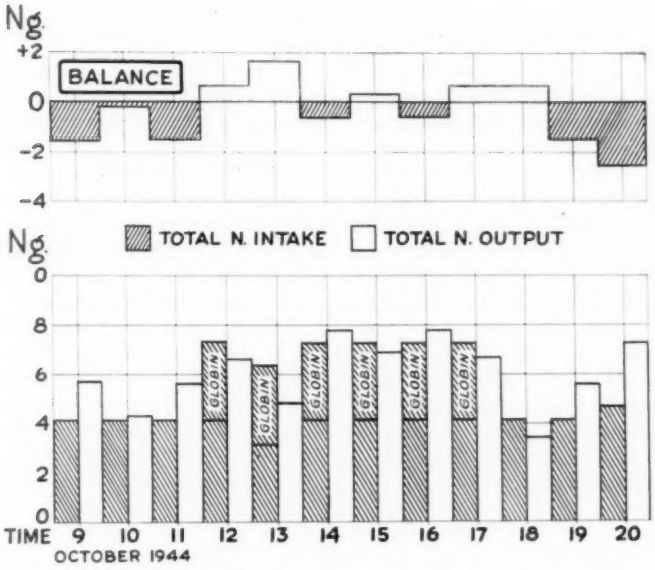


FIG. 1.—Nitrogen intake and output and balance in Case 2.

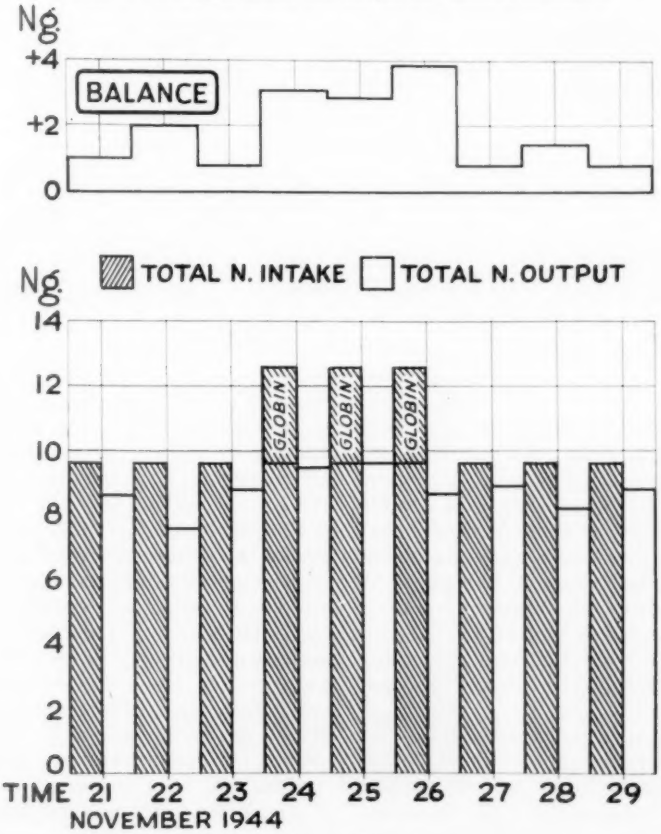


FIG. 2.—Case 2.

fluid intake was maintained constant at 2500 cc. per diem, which resulted in a fairly constant urinary output of about 1500 cc. daily. When intravenous feeding was given, the fluid intake by mouth was cut down accordingly. The results are shown in Figure 3.

It will be noted that the daily intravenous administration of globin solution containing 8.6 gm. of nitrogen caused a sharp reversal of the N balance, which became definitely positive. When the intravenous feeding was stopped the N balance became once again strongly negative. As a control, this experiment was repeated using orally globin and a casein hydrolysate (Casec). Similar results were obtained, although globin by mouth did not appear to be as effective as when administered intravenously.

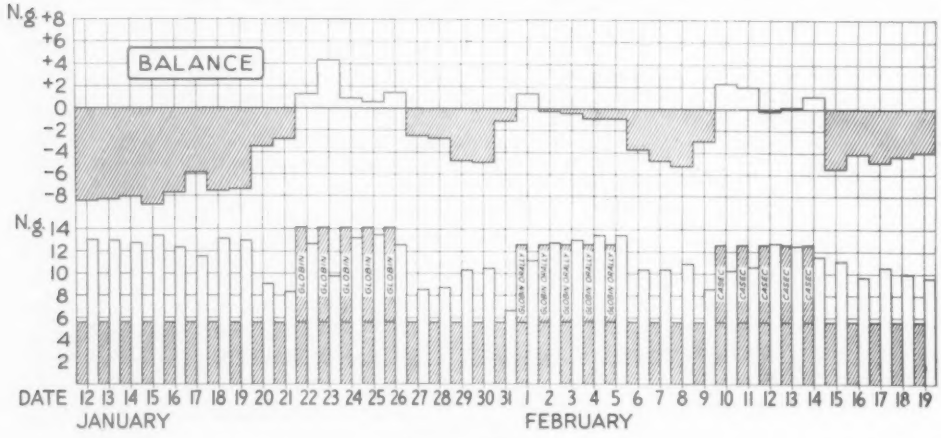


FIG. 3.—Case 3.

On a standard weighed diet with a N intake of 5.6 gm. a day, the determination of the total circulating protein, before the injection of globin was begun, gave a value of 219 gm. Upon the administration intravenously for 5 consecutive days of a globin solution with a daily content of 8.6 gm. of N, the plasma protein concentration remained the same (7 gm. before inoculation, 7.1 gm. after inoculation) but the total circulating proteins rose sharply to a peak of 309 gm. (Fig. 4).

The patient apparently utilized for the production of plasma protein alone 90 gm. of globin out of a total of 260 gm. injected or a ratio of better than 3:1. This represents a good utilization, somewhat better than that reported by Whipple in doubly depleted dogs.[6]

On the 4th day following the last of the intravenous injections of globin, the total circulating proteins were already declining.

CASE 4. R. B., a white woman, aged 59, suffering from carcinoma of the rectum extending into the vagina. Symptoms of bleeding had been present for over 1 year and during this period the patient lost approximately one-third of her total body weight. Prior to an abdominal perineal resection on March 21, the patient was given numerous whole blood transfusions in preparation for the operation. Following the operation, she was given crystalloids, plasma and globin as well as 200 cc. of packed resuspended erythrocytes, as shown in Figure 5.

During the 8-day period from March 23 to March 30 inclusive, the patient received nothing by mouth. Intravenously she received 4200 cc. of globin solution containing 168 gm. of proteins and 3000 cc. of plasma containing a total of 170 gm. of protein. Before the intravenous feeding, the plasma protein concentration was 5 gm.%. On the 8th day, it was 6.1 gm.%. This patient was thereafter maintained on oral feeding and suffered a sharp drop in the plasma protein concentration, which was corrected by additional intravenous administrations of globin and plasma in the ratio of 3:1. The patient made a satisfactory recovery (Fig. 5).

CASE 5. E. D., a 69 year old white woman, was admitted to the hospital April 14, 1945, with complaint of nausea, vomiting, con-

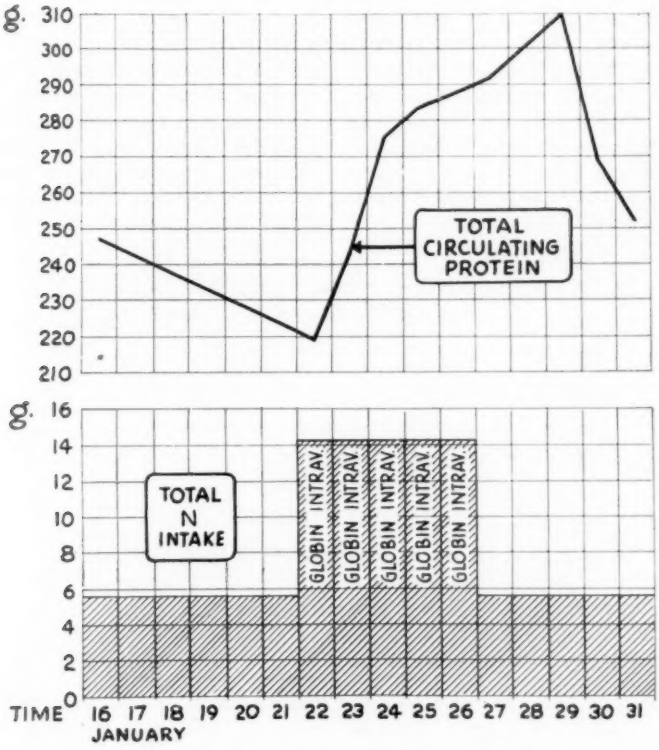


FIG. 4.—Case 3. Circulating protein and N intake.

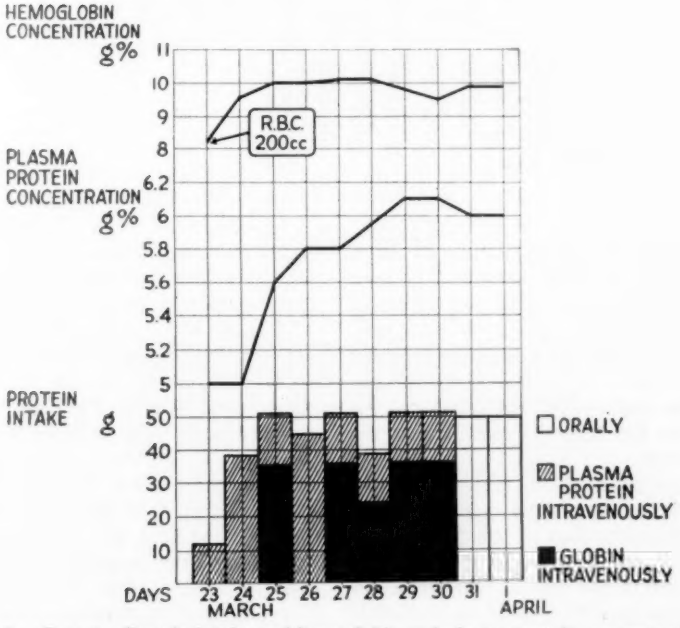


FIG. 5.—Case 4. Protein intake and hemoglobin and plasma protein concentration.

stipation, lower abdominal pain and occasional black stools. The abdominal pain had begun about 2 months before admission and vomiting 2 weeks before. The pain shifted to the epigastrium and for 2 weeks prior to admission the patient retained practically no food and little fluid. One week before admission, the bowels became obstipated, and 2 enemas gave no relief.

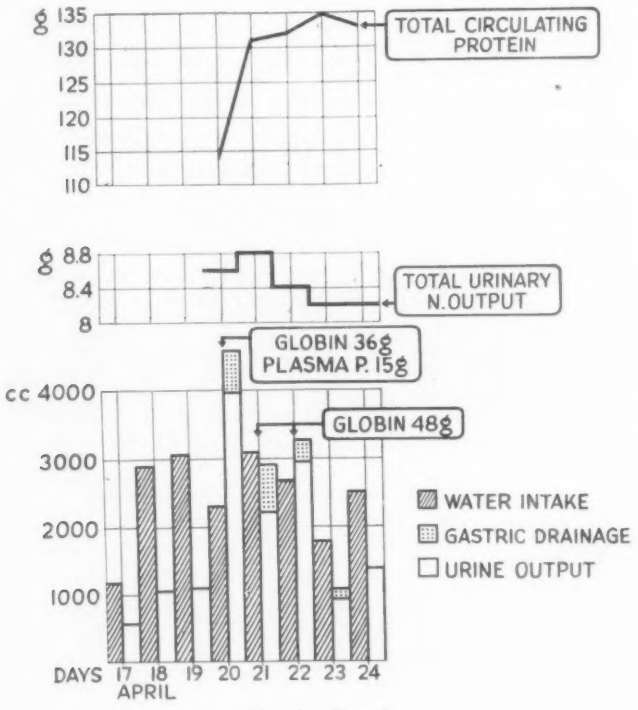


FIG. 6.—Case 5.

On admission the patient appeared dehydrated, and had no visible edema. The liver was palpable 2 fingers breadth below the costal margin and the urinary output was very scanty. Abdominal distention appeared the day following admission, while vomiting continued. The diagnosis of low intestinal obstruction was made, later confirmed at the operating table.

The hemoconcentration and hypochloremia existing on admission were corrected with the administration of 2% NaCl solution. During the 3 days preceding globin administration, there was a positive water balance. Allowing 700 cc. daily for insensible losses, the patient retained 2340 cc. of water during this period. In the 3-day period while globin was administered, there was a good diuresis with a negative water balance resulting in the loss of 4680 cc.

During and following the administration of globin, the urinary N output remained constant. The plasma volume as determined by the dye method (T-1824) and daily hemoglobin determinations showed a sharp increase following the injection of globin. The total circulating proteins showed likewise a sharp sustained increase (Fig. 6).

CASE 6. C. G., a 53 year old white male, suffering from recurring gastric ulcer over a period of 10 years. He was first admitted to the hospital in Feb., 1944, at which time it was discovered that he had a fistula between the stomach and the gall bladder. On this occasion the patient received intravenously over a period of 40 days, 126 gm. of globin for the treatment of hypoproteinemia. He returned to the hospital in May, 1945 because of recurring gastric ulcer symptoms. His diet prior to admission had been poor. He was placed on a standard weighed diet,

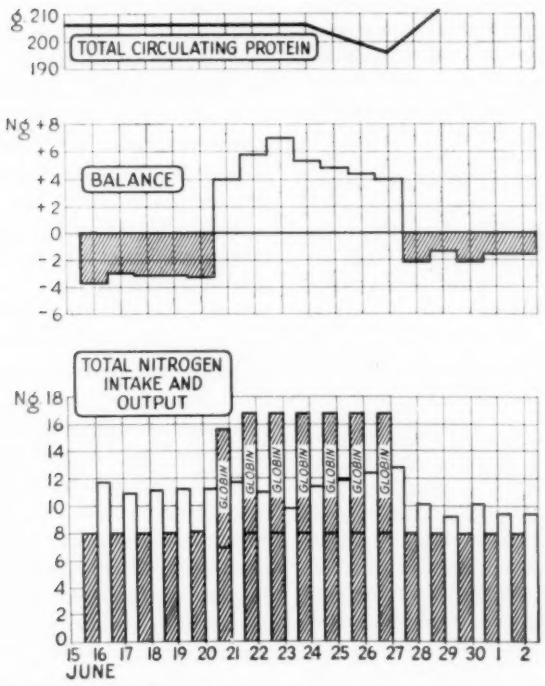
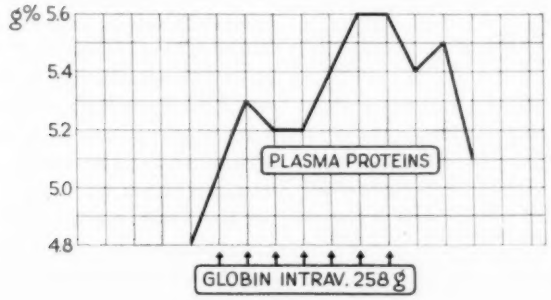


FIG. 7.—Case 6. Circulating protein, nitrogen intake, output and balance.



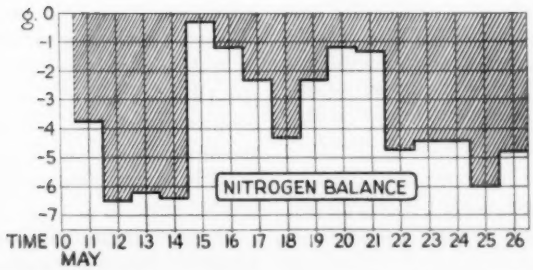


FIG. 8.—Case 7. Plasma protein and N balance.

containing 50 gm. of protein, 80 gm. of fat, and 307 gm. of carbohydrate. In addition, over a period of 7 days, the patient received a total of 370 gm. of globin intravenously. At the time of globin administration, this patient had a normal measured plasma volume and a normal plasma protein concentration. The total circulating protein remained constant at a level calculated normal for his weight and height (Fig. 7). The bulk of the injected globin was retained and apparently was stored as reserve, more exactly, of about 62 gm. of globin N about 18 were used to make up the deficit and most of the remaining were stored. A loss of about 2% of protein in the urine occurred during the globin injection.

Case 7. F. J., a 34-year old white woman, was admitted to the hospital on April 6, 1945 this being her 6th admission. In 1937 she was admitted for treatment of numerous bullet wounds with penetration of the left chest, the stomach, the pancreas, the left kidney, the result of attempted suicide. At that time a mass in the cecal area was found. In 1939 she was operated upon for intestinal obstruction and the terminal ileum with the cecum and half of the colon were resected. The diagnosis of regional ileitis was made. Since that time the patient has suffered from severe hypoproteinemia, with recurring edema and on one occasion, intestinal obstruction.

On May 1, the patient was placed on a weighed diet, consisting of protein 45 gm., fat 70 gm., and carbohydrate 247 gm. With this diet the patient remained in a negative nitrogen balance. From May 15 to May 21, the patient received additionally daily intravenous injections of globin (Fig. 8) totaling 258 gm. Of this protein, the patient used slightly more than half to improve the N balance, although it remained negative; part was utilized to raise the plasma protein concentration from 4.8 to 5.6%. Lipemia prevented an exact estimation of the plasma volume and, consequently, of the total circulating proteins. During the period of observation there was a weight loss of 7 kg., the patient generally being in a negative water balance.

Summary of Cases. Case 1 shows globin utilization in a patient with severe liver damage.

Case 2 is one of severe hypoproteinemia in which a positive N balance cannot be maintained by oral feeding. This is accomplished by additional intravenous globin feeding.

In the same patient, during late convalescence, and while in positive N balance, it is shown that the nitrogen balance can be made more strongly positive by additional intravenous globin feeding. It is presumed that in this patient the reserve proteins were still low.

Case 3 shows that in a patient with a severely negative N balance the bulk of globin N administered is retained and that the balance becomes positive. This is a patient with unquestionably lowered protein reserves. It emphasizes the value of globin in rapidly increasing the volume of circulating proteins in a bed-ridden patient with a low oral protein intake, high nitrogen losses and presumably much lowered plasma protein reserves. The rate of utilization is slightly more than 3:1 for plasma protein formation alone.

Case 4 shows how with plasma and globin a patient can be maintained in the postoperative period, when oral feeding cannot be adequately employed.

Case 5 emphasizes the value of globin in rapidly producing an increase in total circulating protein, with abundant diuresis, amounting to nearly 6 liters of urine in 3 days above the output prior to globin administration.

Case 6 shows that when the circulating plasma proteins are normal, the globin injected intravenously is used in part to make up the deficit in the N balance and the bulk of the remainder is stored.

Case 7 shows that when globin is administered intravenously to a hypoproteinemic patient maintained in a negative N balance, only part is utilized to make up the deficit in the N balance, while approximately half is utilized to regenerate plasma proteins in the circulating blood, the N balance remaining negative all the while.

Because amino acid solutions are somewhat less expensive and more readily available, they should be given the preference

over globin whenever possible.[7] But amino acid solutions frequently give untoward reactions such as pains, vasomotor disturbances, and vascular thrombosis. These reactions can be controlled to a certain extent by reducing the concentration of the solution and decreasing the speed of administration.

A further limitation may be the inability of the patient with even a relatively minor impairment of the liver function to utilize amino acids for the synthesis of protein. Finally, patients with kidney lesions lose the major portion of the amino acids in the urine.

We have in addition noted, as have others[2c,8] that in some hypoproteinemic patients, particularly if the hypoproteinemia is severe, amino acids are not well utilized. If utilization occurs in some of these patients, it represents only a small portion of the total N injected and requires a considerable period of time to produce an increase in the total circulating protein. The following case is typical of this group:

A colored adult male, suffering from duodenal ulcer with gastric retention, received a solution of amino acids* daily from Nov. 1 to Nov. 16 inclusive (1000 cc. of 10% solution intravenously daily or 100 gm. of amino acids containing 12 gm. of N). On Nov. 16, the 24 hour nitrogen output was 15.4 gm.; on the 17th, the day after the administration of Amigen had ceased, the nitrogen output in the 24 hour urine had dropped to 8.2 gm. For the next 5 days, on a constant nitrogen intake by mouth of 8.8 gm., the nitrogen output in the urine remained constant and averaged 8.1 gm. in 24 hours, or nearly 7.5 gm. less than the daily output while the patient was receiving Amigen. In other words, of the 12 gm. of nitrogen which the patient received intravenously daily, over 50% was excreted in the urine. During the 18 day period, in addition to the 12 gm. of nitrogen contained in the amino acid solution, the patient received nitrogen by mouth at a rate of about 4 gm. a day. Before the amino acid administration, the total plasma protein concentration was 5.3. After the completion of the administration of Amigen, the plasma protein concentration was 5.8%.

After a few days this same patient received for a period of 3 days globin intravenously, the dose containing 3 gm. of nitrogen daily. Oral intake of nitrogen at this time was about 9.4 gm. barely sufficient to maintain the patient on an even or slightly positive nitrogen balance. On Nov. 22, the plasma protein concentration was 5.3%. On the 30th, 4 days after discontinuance of the globin administration, it was 6.4 gm.%, the hemoglobin concentration having remained fairly constant during this period of time. Subsequent to the administration of globin, the patient received intravenously for 4 consecutive days 600 cc. of 5% amino acid solution (30 gm. of amino acids containing 3.6 gm. of nitrogen) while maintained in a slightly positive nitrogen balance by the constant oral administration of about 9.4 gm. of nitrogen per day. The additional intravenous feeding of amino acids did not increase the plasma protein concentration which was 6.4 before the amino acid administration and 6.3 after. During this period of time, the hemoglobin concentration remained constant. However, the amino acid administration again definitely increased the urinary nitrogen output. This patient did not have clinical evidence of hepatic insufficiency nor of renal lesion.

Discussion and Conclusions. Although plasma may be regarded physiologically and pharmacologically as the ideal material for intravenous nitrogenous feeding, it is difficult to obtain the quantity generally needed for the care of severely hypoproteinemic patients. Thus for the preoperative and postoperative care of a severely hypoproteinemic patient, who can take orally only a relatively small amount of food, a minimum of 700 gm. of protein intravenously are required as an average. In terms of citrated blood plasma with an average content of 5.5% of protein,

* Amigen, Mead Johnson Co., Evansville, Ind.

this means nearly 13 liters of plasma or about 53 donors. Often, as a compromise, plasma is used in quantity well below the optimal for intravenous nitrogenous feeding.

Of about 19 gm. of protein contained in 100 cc. of blood, only 3 gm. are utilized when plasma is separated and the red cell residue discarded. With the preparation of globin from the discarded cells, approximately 4 times as much protein can be made available from the same quantity of blood.

Plasma should be used preferably in those patients who, with or without hypoproteinemia, have disturbances which are aided by specific substances contained in the fresh or properly preserved plasma. This is particularly true of patients suffering from infection or hemorrhagic diseases.

Preliminary studies have shown that from the standpoint of nitrogenous intravenous feeding, modified globin can be adequately used to replace plasma. It has been our practice in these studies to use either globin alone or 1 part of plasma to 3 or 4 parts of globin. Our experience with amino acid solutions when compared with either plasma or globin is that it is decidedly less effective particularly in the severely hypoproteinemic patient and when time is limited. Amino acid solutions cannot be used in a patient with kidney damage or liver damage. Amino acids appear to be of benefit in maintaining a positive nitrogen balance in patients whose total circulating proteins and the protein reserves are not too low or have been raised by other means.

Whipple,[6] in the doubly depleted dogs, has found that the utilization of modified human globin is good, there being produced during the period of injection about 35 gm. of hemoglobin and 24 gm. of plasma protein, the total injection being 168 gm., a ratio of approximately 3:1. This, notwithstanding the fact that the dog responds unfavorably to the administration of globin from human erythrocytes, and remains in a definitely negative N balance. We have found that in the human definite increase in the circulating plasma protein and in the hemoglobin occurs upon administration of globin intravenously even when the nitrogen balance is negative (see Case 6). In the human, however, there is no reaction to the administration of globin to confuse the picture. In the human, the utilization of globin for plasma protein production is about 3:1.

We wish to emphasize the importance of maintaining the patients in a full caloric requirement, otherwise the utilization of globin or any other nitrogenous food for the production of plasma proteins is reduced.

In our studies in intravenous nitrogenous feeding with plasma, globin and amino acid solutions, we have been interested in the clinical response of the patient judged by the increased urinary output, increased volume of circulating blood, increased total circulating proteins, N balance, improvement in the clinical course such as amelioration of anemia, reduction of edema, etc.

We have been, however, particularly interested on the one hand in the relationship between intravenous nitrogenous plasma administration and the length of time in which an increased blood volume can be maintained and on the other hand, in the relationship between this time factor and the state of protein reserves.

The critical analysis of our results does not afford definite conclusions on this point.

However, it can be definitely concluded that plasma, globin and amino acid solutions do not have identical fields of clinical application, but that insofar as nitrogenous intravenous feeding is concerned, modified globin solution can be used adequately in place of plasma.

Modified globin can be used intravenously with good results even in the presence of severe hypoproteinemia, reduced plasma protein reserves, liver and kidney damage, conditions in which the use of amino acid solutions intravenously has been found to be of little or of no effect.*

* The authors have placed their conclusions with their discussion under a combined heading.

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FATAL AGRANULOCYTOSIS WITH AUTOPSY FOLLOWING THE USE OF THIOURACIL IN A CASE OF THYROTOXICOSIS

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Although many cases of leukopenia and granulocytopenia complicating the administration of thiouracil in the treatment of thyrotoxicosis have been reported in the literature, only a very few fatal terminations as a result of the agranulocytosis are on record.[1,2,3,4,5] As the use of this drug is still in its investigative stage, it is essential that the profession be advised of its dangerous potentialities. It is with this purpose in mind that we wish to add another fatal case of agranulocytosis following the administration of thiouracil for the treatment of thyrotoxicosis.

Case Report. H. S., 34, was admitted semistuporous on Sept. 6, 1944, at 12:04 A.M. Two days prior to admission, he had developed a sore throat, headache, general malaise and feverishness. The following day his condition grew worse. At 2 P.M. of that day he was seen by a physician. Because of the severe pharyngitis and fever, 102° F. sulfathiazole was prescribed. Five hours later, after he had taken 2 doses of the drug (30 gr.) his temperature rose to 105° F. He developed stupor and slight nuchal resistance. For the past 7 months he was under the care of one of us (M. G. W.) for the treatment of thyrotoxicosis.

On admission to the hospital, he was semistuporous with face flushed, markedly dyspneic, and obviously in acute distress. The temperature was 105° F., pulse 150, respiration 44. The eyes, ears and nose were essentially normal. The pharynx was markedly congested and covered in many areas with a glairy exudate. Slight nuchal rigidity was present. There was no cervical adenopathy. The thyroid was palpably enlarged and soft. The lungs were negative. The heart was rapid, normal in rhythm and not enlarged to percussion. A soft blowing mitral systolic murmur was audible. The abdomen was negative. Bilateral Babinski and Kernig reflexes were obtained.

A provisional diagnosis of meningococcic meningitis complicated by thyroid crisis was made and studies were immediately ordered. Lumbar puncture yielded a crystal clear fluid under increased pressure (260 to 270 mm. of water); a cell count of 27 W.B.C. predominantly neutrophils was reported. Although the physical appearance of the fluid was not in keeping with the diagnosis of meningococcic meningitis, penicillin was immediately administered intravenously at the rate of 300,000 units for the first 24 hours. Parenteral fluids consisting of 5% glucose in normal saline containing 1 dram of Lugol's solution in the first 1000 cc. was also immediately administered. Within 1 hour a hemogram was obtained which revealed a Hb. of 90% with W.B.C. 200 per c.mm. A stained smear revealed 50 lymphocytes only; platelets 200,000 per c.mm. and reticulocytes 0.7%. Because of the marked agranulocytosis the family was questioned further. It was disclosed that for the past 7 months he had been taking a new drug for his thyroid condition. This was verified as thiouracil by his private physician. The patient had presented himself at his office with a typical history of thyroid disease. B.M.R. was +32. Hemogram normal; blood sugar 102 mg. per 100 cc.; blood cholesterol of 180 mg. per 100 cc.; blood pressure 140/70. He was given thiouracil, 0.6 gm. daily, and within 2 weeks he gained 8 lbs. and the basal metabolic reading was found reduced to +19. Repeated white blood counts although normal indicated a slight reduction compared to the initial white count. At the end of 1 month of treatment, all the symptoms were relieved. He gained 24 lbs., his pulse was 80 and his B.M.R. was +14. The thyroid gland was perceptibly large. The widening of the

palpebral fissure was not decreased. He was maintained on 0.1 gm. of thiouracil 4 times daily. On June 8, his B.M.R. was +9. On August 12, he reported that, due to some domestic difficulties, he had undergone considerable mental strain. He had lost 13 lbs. His B.M.R. rose to +27; W.B.C. 5000 (60% neutrophils, 36% lymphocytes). Because of the low white blood count he was given 5 minims of Lugol's solution, t.i.d., in addition to the 0.4 gm. of thiouracil. Ten days later the patient telephoned Dr. Wohl and reported that he felt well and that he had gained 7 lbs. in weight. He was instructed to report for another blood examination, but failed to do so. According to the history obtained from a member of his family, he discontinued all medications of August 29.

It was obvious from what has preceded that we were dealing with agranulocytosis, most likely the result of the administration of thiouracil. Accordingly, in addition to the previously outlined régime the following were added: transfusion of 500 cc. of whole blood; pentonucleotide intramuscularly; leukocytic cream; crude liver; vitamins B and C in large doses; oxygen.

A repeated spinal fluid examination later in the afternoon of the same day revealed a lower pressure (not recorded in figures). A cell count of 3 W.B.C.; total protein 36.3 mg., sugar 77 mg., and chlorides 680 mg. Another hemogram revealed 250 W.B.C. per c.mm.; the differential count remained unchanged. A blood culture was sterile after 24 and 48 hours incubation. Urine contained trace of protein and 2 R.B.C. per H.P. field. Pharyngeal swab and culture revealed staphylococcus and diphtheroids, non-hemolytic streptococci.

His response to treatment was favorable toward the late afternoon of his 1st hospital day. The nuchal rigidity and Babinski reflexes disappeared. He responded to questions sluggishly but rationally. The irritability, however, as well as the restlessness persisted so that he had to be shackled. The pharyngeal exudates practically disappeared. No ulcerations were visible. On the following day, however, in spite of the continuation of the outlined régime he became more toxic and stuporous, sinking into deep coma. Temperature rose to 108° F., pulse and respiration in proportion. He expired at 4 A.M. on September 8 after a hospital stay of 52 hrs.

AUTOPSY. The pertinent findings were slight jaundice, prominence of the eyes, moderate pretibial edema. A moderately enlarged thyroid gland weighing 55 gm. The latter showed histologically areas of focal hyperplasia and focal colloid goiter (distended acini). The viscera showed evidence, grossly and microscopically, of shock. The slide of bone marrow was examined by Dr. Michael A. Rubenstein, Pathologist of the Montefiore Hospital, New York, who gave the following opinion: "The bone marrow is moderately hypoplastic, showing marked decrease of myeloid elements and a relative increase of nucleated red cells with appearance of younger forms of erythroblasts. The increase of red cell series is mainly an apparent one due to disappearance of the white cells." The brain could not be examined.

Comments. It appears clear from the clinical and pathological findings that our patient suffered from agranulocytosis resulting from the administration of thiouracil. Although he also received 30 gr. of sulfathiazole, his clinical symptoms and signs were manifest before the latter was given. Besides, there is to our knowledge no case on record in which the sulfonamides have produced an agranulocytosis in so small a dosage or in so short a period of time. Sulfathiazole was administered at 3 and 7 P.M. The hemogram was obtained 6 hours later.

We believe the agranulocytosis resulted in a lowered resistance to infection with subsequent production of a severe form of acute membranous pharyngitis. This infectious process, in turn, probably aggravated the hyperthyroid state which was complicated by a thyroid crisis which most likely contributed to the fatal termination. Although one may argue that the agranulocytosis could account for the above clinical course, the absence of any ulcerations after the complete disappearance of the pharyngeal membrane, the marked irritability, restlessness, and hyperkineticism during the entire course of his hospital stay, which required shackling

to restrain him even after the use of morphine and other sedatives and the high degree of pyrexia, are points in favor of a superimposed thyrotoxic crisis.

That the administration of thiouracil does not prevent a reactivation of thyrotoxic symptoms, is attested by the recurrence of this patient's symptoms, and by an elevated B.M.R. at the beginning of August 1944 in spite of the continuous intake of thiouracil since the middle of February 1944. One of the cases reported by Paschis[7] and his co-workers successfully prepared for thyroid surgery with thiouracil, died from thyroid crisis on the second day after a subtotal thyroidectomy.

Moore[6] and his associates at the Thyroid Clinic of Massachusetts General Hospital, in a very exhaustive report on their observations on thiouracil, make the following statement: "It should be pointed out, however, that in a few patients"—treated with thiouracil—"even though the basal metabolic level was well within normal limits immediately before operation, there were upheavals of cardiac function and rises of body temperature after the operation, reminiscent of the patient operated upon with active hyperthyroidism."

It is also advisable to stress that agranulocytosis in this case became evident after what appeared to be a successful continuous course of treatment with thiouracil for 6 months. In the case reported by Garcill and Lesses,[3] the drug was administered for approximately 1 year. The dosage of thiouracil was relatively small, yet, there was a sudden explosive manifestation of agranulocytosis.

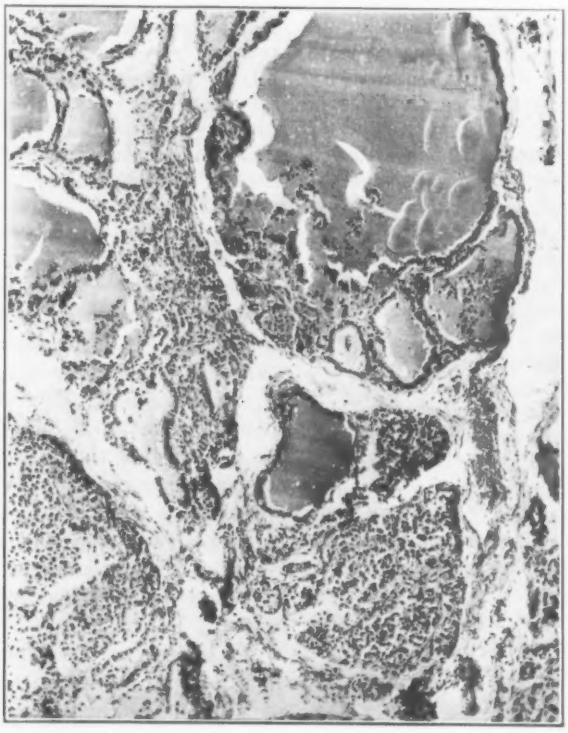

FIG. 1.—Thyroid glands showing areas of hyperplasia and colloid change.

The histologic findings in the thyroid gland are of interest inasmuch as they present a dual picture, one of focal hyperplasia due to thiouracil, and another of

focal colloidal goiter as a result of iodine administration in conjunction with the thiouracil (Fig. 1).

The bone marrow findings (Fig. 2) account for the unusually abnormal hemographic findings—200 W.B.C. per cmm. is the lowest figure so far reported in the literature. Rubinstein[8] reports a study of the bone marrow in a number of patients who developed agranulocytosis as a result of thiouracil and who recovered when the drug was withdrawn. He demonstrated an arrest of maturation associated with hypoplasia of the myeloid elements. Complete hematologic recovery followed the discontinuance of the drug. The return to normal of the bone marrow preceded that of the peripheral blood.

The meningeal symptoms and signs were most probably evidences of meningeal irritation rather than of meningitis. The rapid disappearance of the meningeal signs as well as the rapid decrease of the spinal fluid pressure and the normal cytologic and chemical findings 8 hours after the initial lumbar puncture speak in favor of this opinion.

FIG. 2.—Bone marrow showing area of hypoplasia.

Summary. 1. A case of agranulocytosis resulting from the administration of thiouracil in the treatment of thyrotoxicosis is reported.

2. That the severe infections following the agranulocytosis may result in the reactivation of the thyrotoxic state and be complicated by a thyroid crisis, is stressed.

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THE THERAPEUTIC VALUE OF EARLY PHYSICAL ACTIVITY IN RHEUMATIC FEVER

Preliminary Report

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Rest is the most universally accepted measure in the treatment of rheumatic fever. Rest has been advocated chiefly as a precaution to protect the already damaged heart, or to prevent or minimize its damage, either directly by decreasing the work of the heart, or indirectly in the belief that absolute bed confinement would shorten the illness and thereby reduce the incidence of cardiac involvement. The authors do not dispute the therapeutic value of rest, nor do they advocate an imprudent, negligent régime of early physical activity, particularly in the presence of prominent heart signs or even continuing tachycardia. On the contrary, this paper is an attempt to amplify the term "rest" and to emphasize the value of judicious physical activity as a component part of the therapy of rheumatic fever.

Confinement to bed has always implied the ultimate expression of rest, and as such has been the recommended treatment during acute rheumatic fever. Rest is a relative term. Rest and confinement to bed are by no means synonymous; restriction of physical activity is not necessarily rest. Rest, in our opinion, means maximum ease and comfort, physically, mentally, and emotionally. Bed rest ceases to be rest when the patient is no longer at optimum comfort in his environment. From that point this physical restriction should be termed bed confinement. Prolonged confinement defeats rest, produces restlessness, and thereby increased physical, mental and psychic activity. After prolonged restriction to bed, patients become soma conscious. Symptoms unrelated to the disease assume serious proportions in the mind of the patient (and frequently in the mind of the doctor).

Based on our observations of more than 200 cases of rheumatic fever, it is our opinion that greater rest was obtained by permitting more freedom for activity, such as sitting in or out of bed, and walking to the latrine. Activities were permitted our patients during the acute phase of the disease, usually within the first 24 hours after admission, if their physical discomfort did not prohibit it. Rarely did joint discomfort prohibit ambulation for more than 48 hours when adequate amounts of salicylates were given. Regulated ambulation was permitted in the presence of any cardiac phenomena unattended by congestive failure. The patients were instructed to cease their activities before the appearance of dyspnea, fatigue, or other distressing symptoms. Tachycardia, cardiac murmurs, heart block, subcutaneous nodules, moderate joint pains, rapid sedimentation rates, abnormal electrocardiograms or other laboratory findings indicative of active rheumatic fever or carditis were not used as indications for bed rest or confinement. The patient's comfort alone was the determining factor regarding his bed status and physical activity.

Since the beginning of this study in May 1944, there has been no cause to regret this early physical activity procedure. There have been many favorable results, the most notable, perhaps, being the marked decrease of anxiety neuroses. To date, none of the patients has been

discharged from the service for this reason. On the contrary, these patients have slept more soundly and awakened more refreshed, and the energy expended by tossing and turning in bed has been minimized. Bowel habits have been regular; it has been rare to prescribe a laxative, cathartic, or enema. Consequently, the patients have enjoyed more abdominal comfort, and their better appetites have been reflected by gains in weight. There has been an increased feeling of well being. The morale for recovery has been excellent because the seed of apprehension of long or permanent invalidism has not been allowed to take root. The patient with psychic trauma often has proved more resistant to therapy than one with cardiac damage. The apathy, depression, and resignation effected by traditional therapy have been supplanted by the will to get well.

Management of Patient. *Method.* During the early stage of our program, patients frequently arrived at this hospital after the active phase of rheumatic fever had passed. The number of invalids as a result of cardiac neurosis was impressive. These patients were fearful of participation in any form of physical activity. To gain further insight concerning the cause of this fear, we instructed each patient to write his own history. He was encouraged to write everything which he had thought might have any relation to his illness—the cause, aggravating factors, preceding treatment, and questions regarding his personal prognosis. Our suspicions were confirmed: the fears were the result of the management of the patient rather than of the disease itself. We found that many of these patients had been confined to bed for months; that they had not been permitted to wash, shave, or feed themselves; that they had suffered all other restrictions enforced by a regimen of absolute bed rest; that they had been "listened to every day, blood tested, and electrocardiographed" frequently. In short, they had become the victims of medical science. The disease was cured but the patient was lost. As a result of this well-intentioned management, the rheumatic fever was often replaced by an anxiety neurosis.

When a clinical estimate of the patient's mental and physical pattern had been achieved, management of physical activity was initiated. Appreciation of the severe degree of mental invalidism engendered by therapeutic programs demanding absolute bed rest throughout and beyond the clinical stages of rheumatic fever induced us to adopt certain modifications. Except in cases of heart failure and incapacitating joint inflammation, patients were encouraged to utilize the latrines during the acute stages of the illness. The patient's comfort, not the physical or laboratory findings, was the determining factor that influenced this judgment. Reference to case reports or graphic representations of the course of the disease cannot betray the willingness with which patients accepted latrine privileges, notwithstanding tender, swollen, and inflamed joints. As a rule, severe arthralgias were only of short duration before the full therapeutic effects of salicylates were realized. Such patients then were advised to avail themselves of the lavatory. It should be noted that the distance between the beds and the latrines was made as short as possible.

When the physical comfort had increased, the patient was permitted to sit in a chair for gradually increasing periods of time, provided that the limits of fatigability were not exceeded. As strength returned, ambulation was permitted about the ward and gradually encompassed visits to the ramp and the adjacent lawn. The continuation of the disease process, as revealed by elevated sedimentation rates, high white blood counts, shifts in the Weltman reaction or prolongation of the PR conduction times, was not considered a deterring element. The ward ambulatory stage of physical activity was abandoned, however, when, in the opinion of the observers, any recurrence of incapacitating or painful manifestations appeared. It was contrary to the purpose of the program

to effect any discomfort or pain. In the majority of cases the clinical and laboratory phenomena indicative of acute rheumatic processes diminished and disappeared during the period of physical activity. The patient was then allowed and encouraged to undertake simple handicraft tasks, permitted to leave the hospital on pass for short periods of time, visit other installations on the field when feasible, and attend Red Cross functions. Supervised picnics, overnight passes for the married men living within the confines of the adjacent city, and attendance at various courses under the direction of the military or allied authorities, were included in this stage of convalescence. In all the above phases of physical activity, full therapeutic doses of salicylates were prescribed.

The last phase of conditioning, consisting of graduated exercises, was ordered as the patients were considered fit according to standards established by the AAF Rheumatic Fever Convalescent Program.

Report of Cases. CASE 1. A 21 year old, white soldier, admitted Oct. 16, 1944, with a sore throat and migratory arthritis which involved the right thumb, both knees and the left second metatarsophalangeal joints. During the first 4 days of hospitalization, the temperature fluctuated between 100° F., and 103° F., and the pulse rate between 82 and 120 per minute. Further polyarticular migration involved the various joints of the hands, feet, knees, shoulders and left hip. A satisfactory joint response to salicylates was obtained within 24 hours. A systolic apical murmur appeared shortly after admission but was unattended by any objective or subjective evidence of cardiac or respiratory distress. Latrine privileges were permitted from the beginning of hospitalization and complete ward ambulation was undertaken within the 1st week. At the end of the 1st week the sedimentation rate (Westergren) reached 90 mm. per hour but declined thereafter. The leukocyte count did not exceed 7300, but variations in the amplitude of the T waves, particularly in the second and precordial leads, appeared in serial tracings. Omission of salicylate therapy at the end of the 2nd week was followed by a recurrence of frank polyarthritis; the findings pertaining to the heart remained unaltered. Improvement again ensued upon salicylate administration and, in spite of an elevated sedimentation rate, an inconstant murmur, the indeterminate electrocardiographic changes, physical activity was undertaken in a graduated manner. The sedimentation rate returned to normal levels during the 4th week while the patient was ambulatory about the ward and the hospital grounds. The patient $6\frac{1}{2}$ weeks after the onset of the illness voluntarily rode a bicycle 30 minutes without experiencing any distress or fatigue.

It is to be noted that while the patient increased his physical activity, the signs of acute and latent rheumatic processes diminished. Examination of the subject 6 months after the onset of the illness failed to disclose any cardiac or other abnormalities.

CASE 2. (Figures 1 and 2.) A 25 year old, white soldier, admitted April 21, 1944, with articular symptoms involving both feet, shoulders and elbows. At the age of 8 years he had polyarthritis which prevented activity for a period of 6 months. The temperature was 102.4° F. on admission, the pulse 108 per minute, and the white blood count 6600. A Grade 1 systolic murmur was heard to the left of the sternum and transmitted to the apex. Migratory symptoms affected the knees and ankles. Administration of sodium salicylate produced a rapid remission. The sedimentation rate declined from the previous level of 53 mm. per hour, but failed to return to normal. Reactivation was manifested by a secondary rise of the sedimentation rate, an invasion of the joints, and numerous crops of subcutaneous nodules of the hands, scalp and feet. The cardiac manifestations remained limited to the apical systolic murmur. Although the dosage of salicylates was increased, a left pleural effusion appeared. An apical diastolic murmur became audible during the 9th week, and basilar systolic and diastolic murmurs appeared during the 15th week. No signs of congestive failure could be detected at any time. For the first 16 weeks of hospitalization, the patient remained at absolute bed rest. Transfer to an area of low incidence of rheumatic fever was effected on the 17th week of the illness. On admission, the subject appeared acutely ill, the temperature was 102° F., and the pulse rate 146 per

minute. Bilateral pleural effusion, confirmed by roentgenograms, and apical systolic and diastolic murmurs were present. The cardiac silhouette and electrocardiographic tracings were normal on admission and throughout the hospital stay. The sedimentation rate was 68 mm. per hour; the white blood count was 7200, and numerous subcutaneous nodules were observed over the dorsa of the hands. Therapy with salicylates, sodium bicarbonate, magnesium carbonate, and, later, acetylsalicylic acid was prescribed. Physical activity was permitted despite the acute manifestations. During the 25th week of the illness, when salicylate therapy was stopped, there appeared a recurrence of severe tachycardia, an elevation of the sedimentation rate, and a left pleural effusion. The response to readministration of salicylates was prompt. Physical activity was briefly limited by the patient's symptoms.

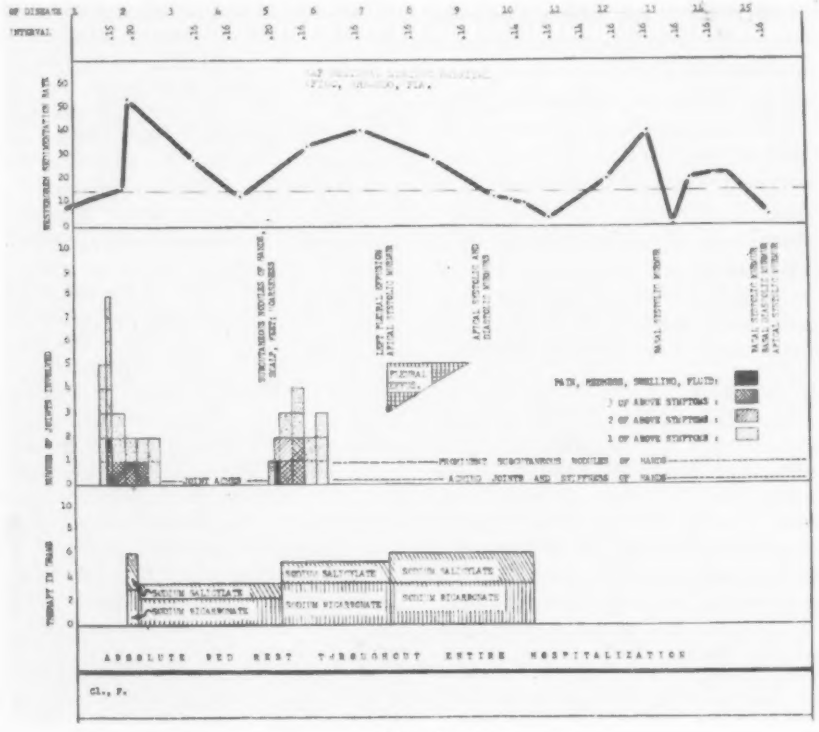

FIG. 1

It is significant that the course of illness after the 17th week was attended by a decrease in the size of the heart. A decrease in the size and the number of subcutaneous nodules of the hands, a gain in weight, and a diminution of cardiac murmurs made their gradual appearance; only a persistent systolic murmur remained as residual cardiac evidence and at no time did the heart show any loss of reserve for ordinary ambulatory activity. The pleural effusion resolved completely and the sedimentation rate declined to normal in spite of progressively increased physical activity. In this case, the reactivation of the rheumatic process during the 25th week of the illness can reasonably be attributed to the cessation of salicylate therapy and not to increased ambulation.

At the time of discharge a Grade 2 apical systolic murmur was the only recognizable evidence of cardiac damage. There was no indication of decreased cardiac reserve. The heart size and electrocardiographic tracings were normal.

CASE 3. (Figure 3.) A 24 year old, white soldier was hospitalized during the latter part of May 1944, for fever, sore throat, and

a cutaneous eruption, which was considered scarlet fever although peeling of the skin was not observed.

On July 2, 1944, he was readmitted for a nasopharyngitis followed in a few days by a migratory polyarthritis that involved the shoulders, knees, elbows and ankles. During the first 72 hours the maximum temperature was 101° F., and the maximum pulse rate was 94 per minute. The sedimentation rate was 54 mm. per hour and remained near that level during the first 6 weeks of absolute bed confinement. The white blood count was 9300, and other laboratory findings, including electrocardiograms, were normal. Administration of 6 gm. of sodium salicylate daily gave a satisfactory symptomatic response, but joint swellings persisted for 2 weeks. A constant apical systolic murmur became audible at the end of the 3rd week and subsequently subcutaneous nodules were found on the right hand and elbow. He lost 10 pounds during this period.

Transfer to this hospital was effected on Aug. 20, 1944, at which time the left knee was swollen. The temperature was 100° F., the pulse rate was 104 per minute, the leukocyte count and the electrocardiograms were normal. Salicylates (10 gm.) were given daily and latrine privileges granted in spite of a mitral systolic murmur and elevated sedimentation rate of 79 mm. per hour. Although the patient's ambulation was increased in proportion to his physica comfort, the sedimentation rate declined satisfactorily, and both the murmur and subcutaneous nodules were gone after 7 weeks of ambulatory therapy. There was no recurrence after cessation of salicylate

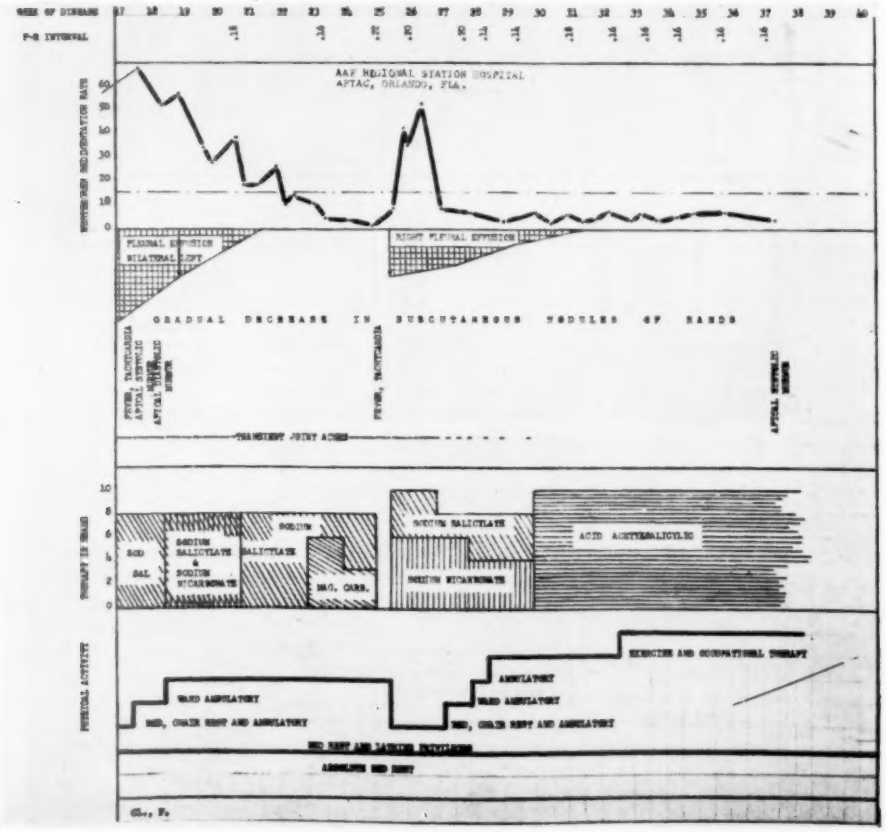

FIG. 2

therapy, and he regained his 10 pounds of lost weight.

The patient made an uneventful recovery, and completed the 6 phases of the AAF Rheumatic Fever Physical Training Program without interruption. He was discharged to duty without residua of rheumatic fever. It is worthy of note that increased physical activity did not prevent or postpone a complete recovery from the acute illness and did not produce any complications or permanent injury.

CASE 4. A 32 year old officer was admitted Aug. 26, 1944, 1 month following an acute tonsillitis. On admission, the patient was acutely ill with involvement of the heels, ankles, knees and shoulders to such a degree that turning in bed was impossible. The tonsils were hypertrophic and acutely inflamed. After 24 hours, abdominal distention, dyspnea and cyanosis appeared, and additional joints became involved. Oral salicylates were stopped because of vomiting; the patient was critically ill and was placed

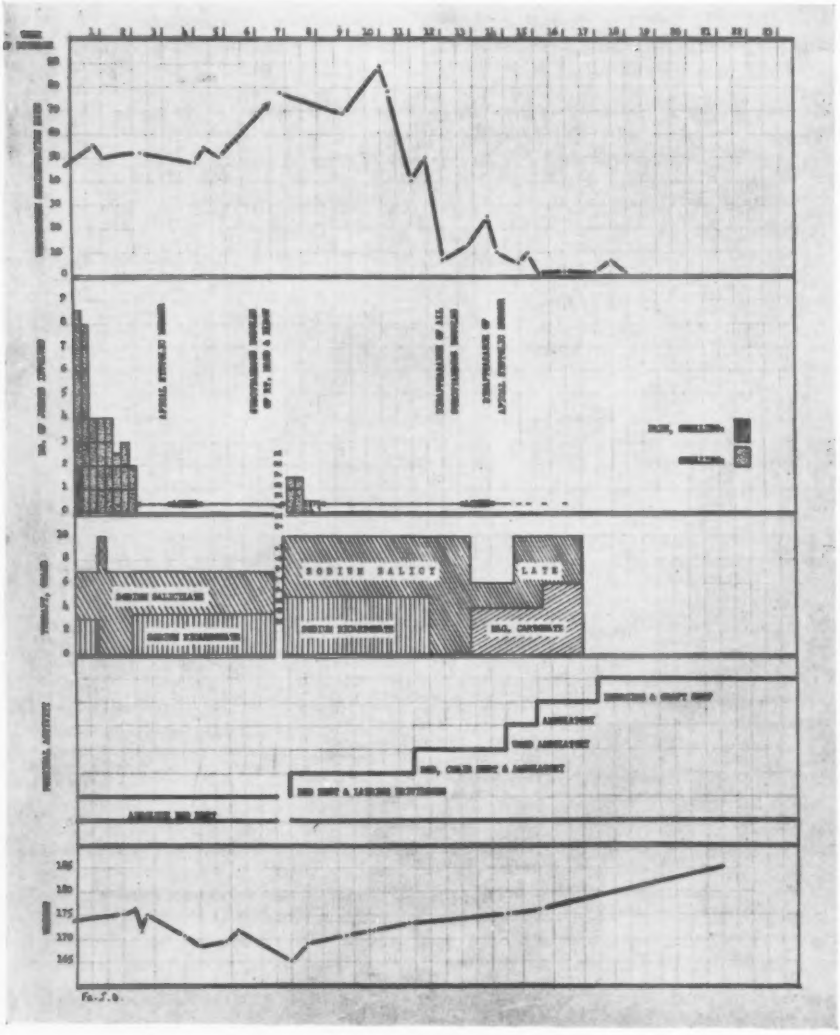

FIG. 3

in an oxygen tent. On the 3rd hospital day there was a pericardial friction rub and physical signs of pneumonitis at the lower lobe of the right lung. On the 4th hospital day there was evidence of a pericardial effusion, a right pleural effusion, a diastolic gallop rhythm, slight edema of the ankles, and marked abdominal distention. Additional signs of circulatory failure were dyspnea, cyanosis, and venous congestion. The left cardiac border, by percussion, measured 14 cm. to the left of the mid-sternal line. Electrocardiograms showed sinus tachycardia with rate of 135 beats per minute, normal axis, low voltage of QRS complexes, large Q_3 (6 mm.), elevation of ST_1, ST_2, and inversion of T_3. Subsequent electrocardiograms during the 1st month of the disease showed flattening of the T waves in the standard leads. There was no improvement in the patient's clinical condition until the use of intravenous sodium salicylates on the 14th hospital day. Within 24 hours there was an increase in the urinary output and a decrease in the abdominal distention. With the continued use of salicylates, the right pleural effusion rapidly disappeared and the pericardial effusion diminished. For one period of 24 hours when the patient did not receive salicylates there was a rapid return of joint phenomena. These responded promptly to the readministration of salicylates. On the 16th hospital day the patient was able to sit up in bed. From the 17th day of his illness the patient was allowed to sit in a chair in addition to latrine privileges.

The above phenomena occurred during the 1st month of illness. The temperature varied from 100° to 104° F. for 24 days. Laboratory findings during this period were: sedimentation rate varied from 70 to 105 mm. per hour; urea nitrogen (on admission) was 61 mg. %; electrocardiograms were consistent with pericardial effusion; and maximum white blood count was 18,300; bedside roentgenograms confirmed the diagnoses of pericardial effusion, right pneumonitis, and right and left pleural effusions.

The 2nd month of his illness was one of progressive improvement. The left pleural effusion which developed about this time responded favorably, the pericardial effusion entirely disappeared, and the right pneumonitis was practically cleared by the end of the 2nd month.

From the 3rd month, all physical and laboratory findings, including electrocardiograms, returned to normal except for a moderate tachycardia. The occurrence of an acute nasopharyngitis on Oct. 9, 1944, was followed by 3 inflamed joints on October 15, which persisted for 2 days and responded promptly to salicylates. Since December 29, the patient progressed in the physical reconditioning program. Four months following discharge to duty, or 10 months after onset of illness, there were no sequelæ.

Summary and Conclusions. This paper is a preliminary report of observations made on 200 patients on whom the diagnosis of acute rheumatic fever was made by the clinical and laboratory criteria recommended by the Army Air Forces. From this study we have been impressed by two things: first, the high incidence of anxiety neuroses, often to a disabling degree; and second, the fact that prolonged bed rest was not necessary for an uncomplicated rapid recovery. Furthermore, early ambulation has greatly reduced the incidence and severity of the anxiety neuroses. The usual clinical and laboratory criteria for judging activity of the disease were not regarded as contraindications for starting early ambulation —the patient's physical comfort was the determining factor. Four case reports are included which illustrate our present program.

We recognize that this study does not warrant any dogmatic conclusions at this time; nor do we advocate indiscriminate physical activity. Nevertheless, it does invite attention to reëvaluation of the currently accepted policy of prolonged bed rest, with its disadvantages, in the treatment of acute rheumatic fever.

THE RELATIONSHIP OF BLOOD PRESSURE AND SERUM THIOCYANATE

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Thiocyanate (sometimes termed sulfocyanate) has been used as a hypotensive agent in patients with hypertension for more than forty years. Early workers, however, found it so highly dangerous that its use was virtually discontinued until Barker (1936)[1] repopularized it by pointing out the simple fact that serum levels could be used to determine the desirable level of dosage and to offset the dangers of overdosage. It has since been widely used and many reports of its clinical efficacy in suitable cases have appeared. The manner in which improvement is brought about by this drug in hypertensive subjects has not been clear. It has long been appreciated that thiocyanates are a normal constituent of the extracellular fluids. Nichols[7] regarded the salivary glands as their chief site of formation. He considered that they were secreted into the saliva, swallowed and absorbed into the "system" appearing in tears and gastric juice. Sollman[8] states "small quantities of thiocyanate are formed from the cyanide which arises in the metabolism of protein or which may be introduced in tobacco smoke or with vegetables such as succotash and onions. It is found in the blood and all body fluids in fairly equal concentration, about 0.03 to 0.06 mg. per 100 ml., and is excreted in the urine and feces, generally in the ratio of 1:2."

In 1942, Caviness and his associates[3,4] reported studies on 241 persons who had never received thiocyanates therapeutically. They found blood serum levels ranging from 0.31 to 2.55 mg. per 100 ml. (estimated as potassium thiocyanate). Furthermore, they observed ". . . all cases presenting high blood pressure fall in the low sulfocyanate concentration group; while in the high blood sulfocyanate group, no hypertension cases appear. Above a concentration of 1.54 mg. per 100 ml. no diastolic pressures above 90 mm. were found, and the only systolic pressures above 130 mm. were one of 150 mm. and one of 138 mm."

The conclusions drawn by Caviness are best stated in his own words: "This work shows that low blood pressure is associated with a high average blood sulfocyanate concentration, that high blood pressure is associated with a low average blood sulfocyanate concentration, and that borderline and normal pressure cases occupy intermediate positions; and it suggests very strongly, even if it does not prove, that sulfocyanates are nature's depressor substances which help to stabilize the balance between hypertension and hypotension."

More recently, Trasoff and Schneeberg[9] reported a survey of 95 hospital in-patients in which the average value was 1.31 mg. KSCN per 100 ml. of blood serum (range 0.84 to 2.40). However, while these values agree closely with Caviness' study, no constant relationship between the height of the blood pressure and the level of the blood sulfocyanates could be demonstrated. Trasoff and Schneeberg concluded, "we cannot regard the blood sulfocyanates as naturally occurring depressor substances nor can we regard sulfocyanate therapy in hypertension as a form of substitution therapy for a substance that, because of a deficiency in the blood, has

allowed various pressor substances to act uninhibited. . . ."

It seemed important to us to decide which of these conflicting views were correct. Caviness' ideas, if acceptable, are basic to our understanding of the pathogenesis of hypertension, and he has advocated the therapeutic use of thiocyanates in small doses more or less prophylactically in the very earliest stages of asymptomatic hypertension. Accordingly, the following investigation was undertaken:

Method. Our survey covers 341 subjects composed of students from the 1944 freshman class of Queen's University, patients from the Ontario Mental Hospital, Kingston, in-patients at the Kingston General Hospital and patients from private practice. There were 268 males and 73 females; ages ranged from 16 to 84 years. Because of obvious sources of error, patients in cardiac decompensation, in shock, or suffering from myocardial infarction or febrile illnesses were excluded from the study. A mercury column sphygmomanometer was used for all blood pressure readings. With a few exceptions, these were made on the left arm with the subject in a supine position. Readings were repeated during the examination until the levels stabilized within a range of 4 mm. The systolic and diastolic pressures recorded are those of Phase I and Phase IV respectively.[2] Subsequently the blood specimen was taken for chemical analysis. No attempt was made to regulate the diet, smoking habits or physical activity of the subjects.

Technique. To 3 ml. of blood serum was added an equal volume of 10% trichloracetic acid. This mixture was agitated thoroughly, allowed to stand 10 minutes, centrifuged for 20 minutes at 2000 r.p.m. and filtered. To 3 cc. of the protein-free filtrate were added 0.5 ml. of ferric chloride indicator and 6.5 ml. of distilled water. The resulting pinkish-yellow solution was then estimated in a Cenco-Sheard-Sanford photelometer using a filter with maximum transmission of 400 μ. The accuracy of our work was checked periodically by recovery tests.

Results. The average value of serum potassium thiocyanate for the 341 cases studied was 0.79 mg. per 100 ml., with a range of 0 to 2.77 mg. per 100 ml. The standard deviation of this group was 0.6 which means that two-thirds of the group fall within the interval 0.19 to 1.39 mg. per 100 ml.

Among 20 hypotensive subjects with an average pressure of 99/61 the average serum potassium thiocyanate concentration was 0.47 mg. per 100 ml. (range 0 to 1.21). Among 192 normotensive subjects, average pressure 120/69, the average serum concentration was 0.84 mg. per 100 ml. (range 0 to 2.77). In the borderline group, average blood pressure 137/74, 42 patients had an average serum level of 0.78 mg. per 100 ml. (range 0 to 2.10). In the hypertensive group, 66 subjects with an average blood pressure of 165/95 possessed an average thiocyanate value of 0.73 mg. per 100 ml. (range 0 to 2.20). In the group of 21 severe hypertensives whose average pressure was 228/131, the average thiocyanate concentration was 0.80 mg. per 100 ml. (range 0 to 2.10). The relationship of these diastolic blood pressures and serum potassium thiocyanate concentrations is shown graphically in Table 1.

(In plotting thiocyanate values against diastolic pressures, instead of against systolic pressures, we are following the precedent of Goldring and Chassis[5] who believe an elevated diastolic pressure of more diagnostic significance in evaluating arterial hypertension than the systolic pressure. Actually, there was no essential difference in the appearance of our two graphs when systolic pressure was interchanged with diastolic pressure in constructing the ordinate.)

In this investigation of 341 subjects, the correlation coefficient of thiocyanate concentration and diastolic blood pressure was $-.13$, and the standard error 0.054. The square of the correlation coefficient was 0.017.

Discussion. A very slight inverse correlationship is demonstrated between these two variables. However, the coefficient of -0.13 is practically mid-way between $+1$ and -1, which signify perfect positive and negative correlation respectively, and zero which designates complete absence

TABLE 1.—AVERAGE VALUES OF GROUPS CLASSIFIED ACCORDING TO THE CRITERIA OF TRASOFF AND SCHNEEBERG

Group	No.	Blood pressure		Age	KSCN (mg per 100 ml.)
		Systolic	Diastolic		
1. Hypotension (below 106 systolic)	20	99.3	61.2	40.8	0.465
2. Normotension (107 to 130 systolic)	192	119.7	68.7	26.7	0.836
3. Borderline (131 to 140 systolic)	42	137.1	74.0	30.2	0.784
4. Hypertension (141 to 200 systolic)	66	164.9	95.0	45.0	0.727
5. Severe hypertension (over 200 systolic)	21	227.5	131.0	56.6	0.803

of correlation. Moreover, the coefficient of correlation must be squared to show the percentage of explained variation. This is 0.017, or an explained variation of less than 2%, which is so slight that it is insignificant. Indeed, it might be due quite as well to a normal sampling error as to a stable correlation.

Examination of the graph reveals a simple scatter distribution of data. This distribution resembles closely the results published by Caviness. Although the latter concluded that "the average blood sulfocyanate level for each blood pressure group varies inversely with the blood pressure," the graph of his results is so similar to ours that we believe it to be statistically insignificant also. If the correlation coefficient for his data were calculated, it is very doubtful that it would exceed -0.2 in magnitude.

The graphic picture of Caviness' findings conveys a false appearance of an inverse correlation because his graph is rectangular, not square, the abscissa or y-axis being almost twice the length of the ordinate or x-axis. This arrangement tends to cluster points along a regression curve sloping downwards from right to left. Furthermore, Caviness' two groups of hypotensive and borderline subjects are so small (9 and 19 at the prison and 10 and 12 at the State Hospital, respectively) that doubling or trebling the size of these groups might lead to a considerable shift in the averages calculated.

Although Trasoff and Schneeberg published no correlation coefficient, they concluded that there was "no constant relationship of blood pressure to blood sulfocyanate concentration." Our numerical results are parallel to theirs except that our average KSCN values are 0.3 to 0.6 mg. per 100 ml. lower. This could be due to having used a filter of different wavelength, 400μ as compared with theirs of 440 μ. This variation in colorimeters probably explains the zero KSCN values among 47, or 14%, of our subjects.

It must be remembered, however, that the correlation coefficient is a measure of association only; in its interpretation association must not be confused with causation.[6] Although two variables, A and B, may be associated, it does not follow that they are casually related, that a change in A is directly responsible for a change in B and *vice versa*. There may be some common factor, C, which is responsible for their associated movements. For instance, in a series of cities it might be shown that the tuberculosis death rate and overcrowding were correlated with one another. But this is not evidence that tuberculosis is due to overcrowding. Possibly, and probably, cities with a high degree of overcrowding are also those with a low standard of living. Such a third factor may be the one which is responsible for the level of the tuberculosis death rate, and overcrowding is only directly associated with it.

Finally, the statement that sulfocyanates occur "normally" in blood, made by both Caviness *et al.* and Trasoff and Schneeberg, should be challenged. They have assumed that the characteristic pinkish-yellow color reaction after the addition of an indicator, is due to the presence of thiocyanate as a ferric salt. This may well be the case, but an exhaustive search of the literature by us has failed to reveal any report of the isolation of a thiocyanate salt in crystalline form from either human or animal blood. Had our results supported Caviness'

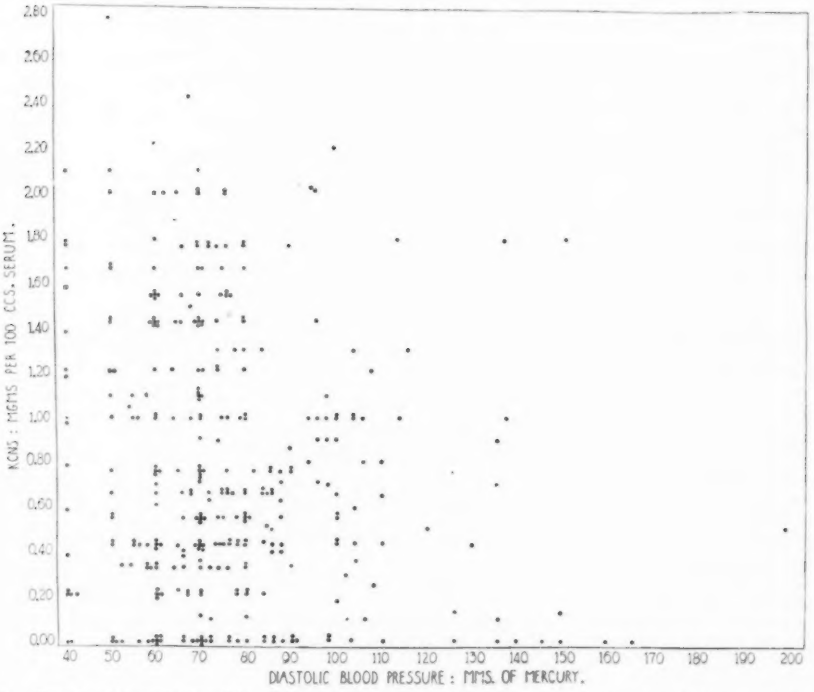

FIG. 1.—Graph of the relationship of diastolic blood pressure and serum potassium thiocyanate in mg. %.

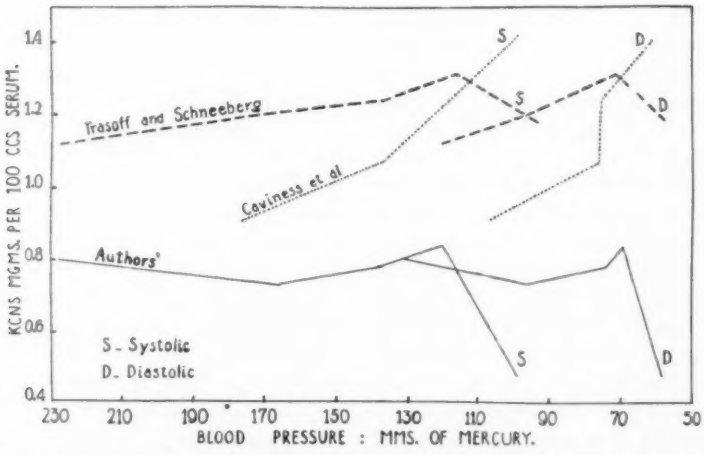

FIG. 2.—Graph comparing the findings of Trasoff and Schneeberg, Caviness *et al.*, and the authors concerning the relationship of blood pressure and serum potassium thiocyanate in mg. %. Each point represents the average blood pressure (systolic or diastolic) and the average serum potassium thiocyanate of a clinical group.

hypothesis of a negative correlation between blood pressure level and blood thiocyanate content, we considered attempting such isolation of a thiocyanate salt by fractional separation of the serum from ox or human blood. In view of our very definite findings of no correlation, we have decided against proceeding with this problem at this time.

Conclusions. 1. A substance, giving the color reactions of thiocyanate, was found to occur in the serum of 341 subjects, not on thiocyanate therapy, in concentrations ranging from 0 to 2.77 mg. per 100 ml. (estimated as potassium thiocyanate).

2. There is no statistically significant relationship between the concentration of this substance and the diastolic blood pressure.

3. Our findings are definitely against the hypothesis that thiocyanate as found normally in human serum has any rôle in the regulation of blood pressure.

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PALMAR ERYTHEMA—ITS RELATIONSHIP TO PROTEIN DEFICIENCY

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Palmar erythema was apparently first distinctly described by Chalmers[5] in 1899. Parkes Weber[17] referred to this as "beer drinker's hands" in 1901. Interest was revived in 1929 when Lane[10] described a familial variety of palmar erythema. Since then several reports have emphasized the coëxistence and possible common etiological relationship between palmar erythema and cutaneous vascular "spiders."[16]

It is now well established that palmar erythema is not a rare clinical finding, and that it frequently is associated with pregnancy,[1,6,11,16] cirrhosis of the liver ("liver palms"),[4,12,13] pulmonary tuberculosis ("'TB' hands"),[15] rheumatoid arthritis, and a wide variety of other diseases.

The authors were impressed with the frequency with which palmar erythema was observed on all the wards of the William J. Seymour Hospital, Eloise, Michigan, particularly in diseases commonly associated with a protein deficiency.

During a period of 13 months (January 1942 to February 1943) 93 instances of palmar erythema were observed in examination of 1183 patients, an incidence of 7.9%. A similar incidence of palmar erythema has been observed in Salt Lake City by one of us (H. H.), while a lower incidence (about 5%) has been noted in Philadelphia (R. J.). The palmar erythema did not differ from that so adequately described by others,[4,16] and often extended to involve the soft tissues of the entire terminal phalanx. Both the mottled and diffuse types were seen with occasional involvement of the soles. Cutaneous vascular "spiders" were frequently observed in these patients.

The ratio of male to female patients admitted to the Seymour Hospital, most of which are adults, is approximately 2 to 1. Children and pregnant women were not included in this study. Palmar erythema was evident in patients suffering from almost every type of disease (see Table 1) and in all age groups (17 to 90 years). It was observed in 2 colored female patients both with hypo-albuminemia, as well as in 3 apparently normal persons, 1 of whom had a hypo-albuminemia. In patients with hemiplegia or with a unilateral deformed hand secondary to rheumatoid arthritis the palmar erythema was usually more marked in the involved side.

The nitrogen determinations were made according to the method of Greenberg,[7] and in 47 patients the total plasma protein concentration was checked with the gravity method of Barbour and Hamilton.[2] Globulin was precipitated out by the sodium sulfate method of Howe.[8] The accuracy of the methods, reagents, etc., was established by determining the albumin and globulin concentration in the plasma of 47 samples of blood collected from 22 patients. Each sample was divided into two or three lots and each assigned new numbers. The chemist who made the analyses was unaware of the origin of the specimens. The variations in values for concentration of the plasma protein in the blood samples were as follows:

Day to day variations in the same patient if the concentration is approximately normal may be greater, but these variations are sometimes seen even with electrophoretic methods and therefore may be assumed to be physiologic.

* This work was done while the authors were on the staff of the William J. Seymour Hospital, Eloise, Mich.

† This work was supported in part by a grant from Frederick Stearns & Co., Detroit, Mich.

TABLE 1.—MAJOR DIAGNOSES OF PATIENTS SHOWING MARKED PALMAR ERYTHEMA

Heart disease:	Cor pulmonale	Myocardial infarction	
	Hypertension	Rheumatic valvulitis	
	Syphilitic aortitis	Subacute bacterial endocarditis	
Arthritis:	Rheumatoid	Mixed	
Neurologic:	Multiple sclerosis	Amyotrophic lateral sclerosis	
	Hemiplegia	Cord tumor	
Psychosis:	Organic	Functional	
Genito-urinary:	Stone	Neoplasm	
	Obstruction	Infection	
Chronic osteomyelitis.			
Carcinoma:	Gastro-intestinal tract	Face	Bladder
	Cervix	Lung	Kidney
Chronic ulcers:	Varicose	Decubitus	Peptic
Burns.			
Endocrine:	Diabetes	Obesity	Hyperthyroidism
Cirrhosis of the liver.			
Blood:	Anemia	Polycythemia	
Vascular:	Arteriosclerosis	Buerger's disease	
Pulmonary:	Pneumonitis	Bronchiectasis, tuberculosis	

TABLE 2.—VARIATION IN VALUES FOR CONCENTRATION OF THE PLASMA PROTEIN IN BLOOD SAMPLE

	Maximum variation	Average variation
Total protein, gm./100 cc.	0.7	0.26
Albumin, gm./100 cc.	0.7	0.25
Globulin, gm./100 cc.	1.2	0.31

The concentration of plasma protein was studied in 73 of the 93 patients. The data obtained from the palmar erythema group were compared with the usually accepted normal values and with those from a group of 40 unselected hospital patients. Three of the 40 control patients had photogenic palmar erythema confirming the over-all incidence of approximately 8%.

Hypoalbuminenia occurred more frequently in patients with palmar erythema (Fig. 1) than in the unselected group of patients. The concentration of albumin in the plasma in approximately 82% of the patients with palmar erythema was below 4.1 gm. per 100 cc. as compared to 62.5% of the unselected patients. Globulin values, as shown in Figure 2, do not deviate from the normal range as frequently as those for albumin. 33% of the patients with palmar erythema and 10% of those in the unselected group show a concentration of globulin above normal, while only 5.5% of the former and 20% of the latter groups gave values below the normal range. This suggests that in patients with palmar erythema the concentration of plasma globulins tends to be increased while the plasma albumin is reduced.

The significance of the difference of the means between the incidence of hypoalbuminuria in patients with palmar erythema and the unselected hospital patients is indicated in Figure 3. As the difference between the two means is more than three times its standard error the chances are more than 99.7 in 100, that the difference is significant.

There is no significant difference between the total plasma protein concentra-

tion of the two groups even though the means of both groups are definitely below the accepted normal range. The albumin concentration in the plasma in the group with palmar erythema is not only below normal but the distribution around a slightly lower mean value is significantly different from that of the unselected group.

In 23 patients with palmar erythema the concentration of amino acid nitrogen in the plasma was found to be normal by the method used.[9]

While the authors wish to emphasize that approximately 80% of the patients with palmar erythema studied had hypoalbuminemia we do not suggest that protein deficiency is the cause of palmar erythema. Many patients with frank protein deficiency do not exhibit palmar erythema, and occasionally palmar erythema may exist in patients without demonstrable protein deficiency.

In only three[4,11,12] of the twenty-one articles published on palmar erythema are

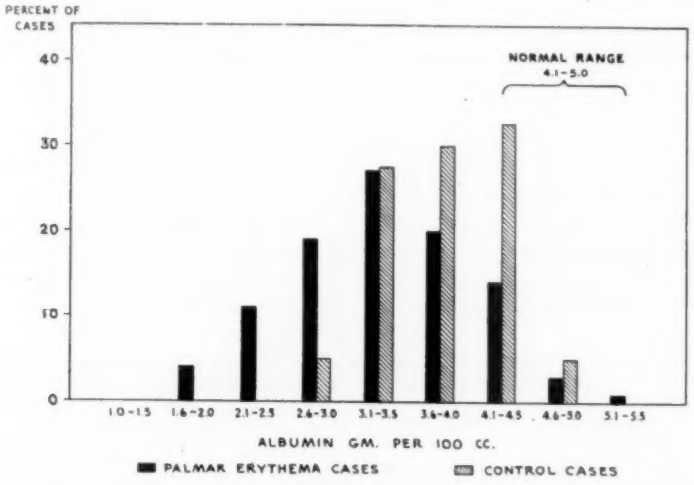

FIG. 1.—Plasma-albumin concentration in 73 patients with palmar erythema compared with 40 unselected patients in same hospital

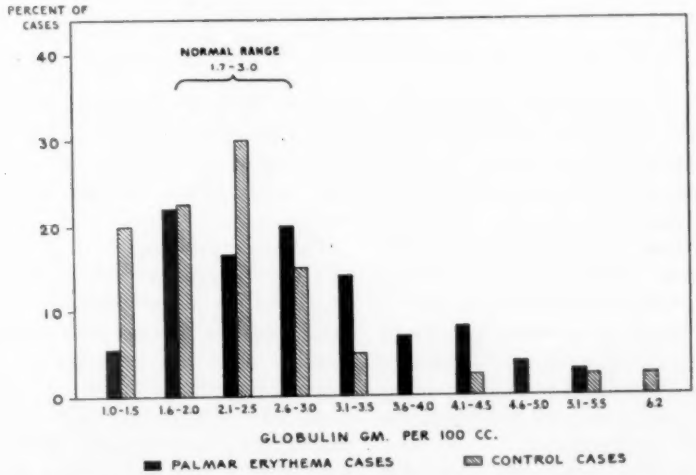

FIG. 2.—Plasma-globulin concentration in 73 patients with palmar erythema compared with 40 unselected patients in same hospital.

there any data given on the concentration of plasma proteins. Two[4,11] give hypoproteinemic values in a total of 3 patients and the other[12] dismisses the question with a statement denying any consistent relationship in 14 cases but gives no data. However, the author does infer that a nutritional deficiency may be a factor.

It is noteworthy that the conditions or diseases in which palmar erythema frequently occurs also are known to exhibit a high incidence of protein deficiency. The incidence of protein deficiency in cirrhosis of the liver, pulmonary tuberculosis, and the latter half of pregnancy is greater than the reported incidence of palmar erythema in these conditions.

Lofgren[11] obtained questionable results following the aministration of estradiold benzoate in 2 patients. Dr. A. Segaloff,[14] who was at Eloise during this study, gave 4 patients 3 to 6 mg. of stilbestrol daily for several weeks. Two of the patients had cirrhosis of the liver, cutaneous vascular "spiders," impaired liver function, and slight palmar erythema. No increase in the palmar erythema was observed. The other 2 patients also had cirrhosis of the liver but did not have vascular "spiders" and no palmar erythema. Stilbestrol did not produce palmar erythema. A fifth patient with marked palmar erythema, cirrhosis, impaired liver function, and hypoproteinemia was given 10 mg. of testosterone propionate per day for 10 days without any change in the palmar erythema.

	NO. CASES	TOTAL PROTEIN GM./100 CC.			STANDARD DEVIATION	STANDARD ERROR
		MIN.	MAX.	MEAN		
PALMAR ERYTHEMA	73	4.2	9.6	6.29	0.70	0.151
CONTROL GROUP	40	5.2	9.4	6.18	0.79	

DIFFERENCE OF MEANS 0.11 NOT SIGNIFICANT

	NO. CASES	ALBUMIN GM./100 CC.			STANDARD DEVIATION	STANDARD ERROR
		MIN.	MAX.	MEAN		
PALMAR ERYTHEMA	73	1.8	5.4	3.35	0.675	0.117
CONTROL GROUP	40	2.9	4.7	3.82	0.524	

DIFFERENCE OF MEANS 0.47 SIGNIFICANCE $\frac{0.47}{0.117} = 3.1$

FIG. 3.—Plasma-protein concentration in palmar erythema compared with control group.

The erythema has been shown to be a result of dilatation of a comparatively rich supply of capillaries in the involved areas.[1,16] At one time or another heredity,[10] endocrine disturbances,[4,11] chronic lung diseases,[15] and nutritional deficiency,[12] have been offered as causative factors of palmar erythema. The adjacent arterioles may also be dilated. The skin covering the involved areas is of normal thickness and histologic structure.

While there has been one successful attempt to accentuate or produce palmar erythema by the injection of estrogens,[3] Palmar erythema is due to a dilatation of the capillaries in richly supplied pads of the hands, fingers and feet. Once the erythema has become well established it usually does not completely disappear when the precipitating causative factor is removed. Palmar erythema appearing during pregnancy usually fades considerably during the postpartum period. In patients with cirrhosis of the liver the intensity of the erythema often decreases

perceptibly when the hypoalbuminemia is corrected and the hepatic function is increased. This suggests that the capillaries dilated under these conditions do not return to their previous normal state even though the dilating agent has been removed.

Impaired liver function is commonly found in patients with hypoalbuminemia. Bean[3] suggests that abnormal metabolism of the 17-ketosteroid hormones may be a causative factor.

Palmar erythema has been observed to occur with equal incidence in both sexes and to have been present at birth and in the 10th decade. While the evidence indicates that the accumulation of excessive amounts of estrogens or 17-ketosteroids in the circulation either because of overproduction or decreased destruction by a poorly functioning liver can cause a sufficient capillary dilitation to result in palmar erythema it does not preclude the possibility of other as yet unknown mechanisms.

Palmar erythema is usually symptomless and does not affect the patients adversely except for its possible conspicuous appearance. Nevertheless, if its true etiology was understood it might have considerable diagnostic significance.

Conclusions. Palmar erythema was observed in 93 of 1183 patients examined.

Palmar erythema occurred in all ages of both sexes studied and in a wide variety of diseases.

Hypoalbuminemia occurred in 83% of the patients with palmar erythema and in 62.5% of an unselected group of patients in the same hospital. This difference is significant.

Hypoalbuminemia is not regarded as cause of palmar erythema; but the finding of palmar erythema in a patient should suggest the probable existence of a protein deficiency.

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A SIMPLIFIED APPARATUS FOR THE INDUCTION OF ARTIFICIAL PNEUMOPERITONEUM

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In a previous article[1] the great utility of this simple diagnostic procedure was discussed, and the use of the Robinson pneumothorax apparatus to induce a pneumoperitoneum was described. Attention was invited to the fact that this afforded the simplest and safest method available:—

1. To determine the presence, position, size, contour, mobility, and attachments of certain abdominal organs (particularly the liver, spleen, stomach and kidneys).

has failed to show a single instance of this serious complication having occurred with the use of carbon dioxide. Experimental evidence supports the contention that this gas is safe.[2]

The technique of inducing artificial pneumoperitoneum has since been further simplified so that it can be performed in the office, clinic, or Roentgen ray department. The use of the Robinson pneumothorax apparatus has been discontinued in favor of a home-made system, which

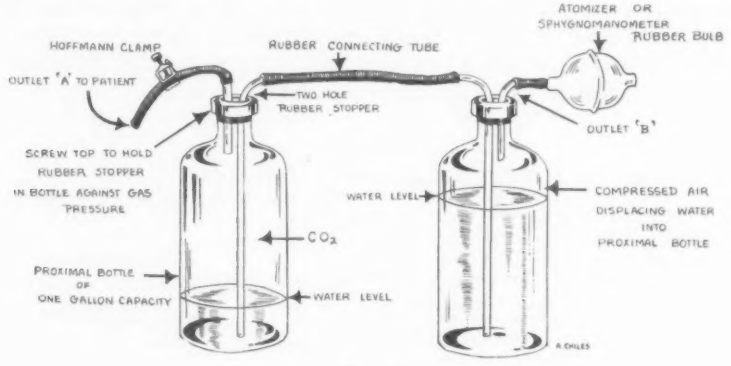

Fig. 1

2. Preliminary to splenectomy, so as to forewarn the surgeon as to whether this organ be adherent, etc.

3. To differentiate between intraperitoneal and extraperitoneal rupture of the urinary bladder.

4. To demonstrate intra-abdominal adhesions.

5. To outline the subdiaphragmatic spaces.

6. In the treatment of tuberculous peritonitis.

It was pointed out that since carbon dioxide had been substituted for air, as the gaseous contrast medium, the danger of gas embolism had probably been eliminated. A follow-up study of this point

has the advantage of greater economy and greater gas capacity. With the former, adequate visualization in patients who had had an ascites of a considerable degree, required the delay and inconvenience of refilling the bottles in order to administer amounts greater than 2000 cc. of carbon dioxide.

The assembly is illustrated in Figures 1 and 2. Initially, the proximal bottle is filled with water. Outlet "A" is attached to a tank of carbon dioxide, the atomizer bulb is disconnected from outlet "B" and the gas turned on. This displaces the water from the proximal bottle over into the distal one, and leaves the former filled with carbon dioxide gas. Outlet "A" is

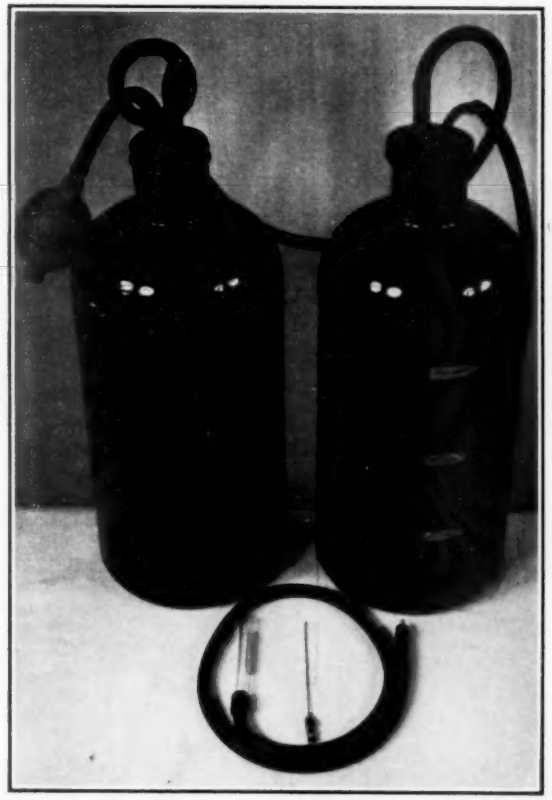

FIG. 2.—Showing how the screw caps to the bottles have been cut out to permit passage of inlet and outlet tubes at the same time preventing pressure within the bottles from blowing out the rubber stoppers. The only part of the unit requiring sterilization is shown at the bottom of the plate.

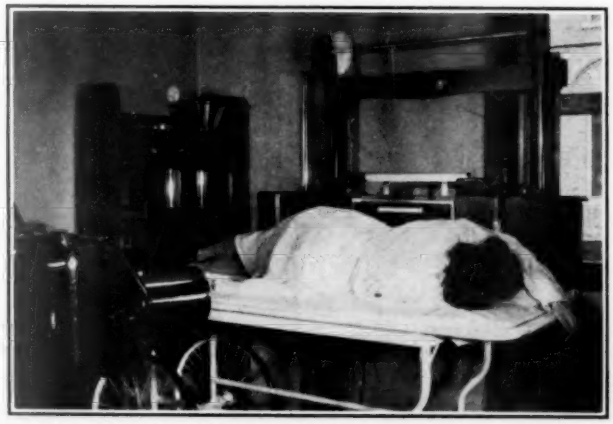

FIG. 3.—The patient lies with right side down in order to visualize the spleen.

FIG. 4.—The patient lies with left side down in order to visualize the liver

FIG. 5.—The subdiaphragmatic spaces are visualized by exposing the film with patient standing.

FIG. 6.—Position of the patient for demonstrating the presence of intra-abdominal adhesions.

closed off with a clamp or hemostat to prevent loss of the gas; the atomizer bulb is re-attached to outlet "B"; and the apparatus is ready for use.

The abdomen is entered in the midline (linea alba), after preliminary surgical preparation and anesthetizing of the site of puncture, by means of a spinal puncture needle. Following entry into the peritoneal cavity, the stilet is withdrawn from the needle, and the latter plugged into the Luer adaptor attached to the sterile unit shown in Figure 2.

By means of the atomizer bulb a layer of compressed air is produced above the water in the distal bottle, which forces this liquid medium over into the proximal bottle. As the water rises up in the latter receptacle, it pushes the CO_2 lying above, out through the sterile unit and into the patient's abdominal cavity. Somewhere between 1500 and 3000 cc. is introduced. Patients who have had considerable ascitic fluid require and tolerate a larger quantity of gas than those who have not had ascites. Obviously this transudate should be largely removed before inducing artificial pneumoperitoneum.

Roentgenograms are taken at 2 meters, for which an upright Bucky diaphragm is useful but not necessary, as we have gotten excellent pictures without its use. The spleen is best visualized by having the patient lie with his right side down, and facing the Roentgen ray plate (Fig. 3). The reverse is used to outline the liver (Fig. 4). The sub-diaphragmatic spaces are visualized by exposing the film with the patient standing erect (Fig. 5). This latter position is also used to determine intraperitoneal rupture of the bladder after having injected the carbon dioxide into the bladder *via* the urethra, rather than through the linea alba. Here the quantity injected is much less—only enough to produce a visible gas shadow beneath the diaphragm. Intra-abdominal adhesions to the belly wall are best shown with an exposure made with the patient lying on his back on the table or stretcher (Fig. 6).

By means of this procedure, malignant and/or other lesions high up in the fundus of the stomach, have also been demonstrated which were not seen at routine fluoroscopy. Artificial pneumoperitoneum is induced after having produced a contrast medium within the stomach (either a thin barium suspension or gas generated by administering a Seidlitz powder will suffice). This places a contrast medium on both the inside and outside walls of the stomach, thereby showing both the contour and thickness of same.

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THE OCCURRENCE OF FIBRINOLYSIS IN SHOCK, WITH OBSERVATIONS ON THE PROTHROMBIN TIME AND THE PLASMA FIBRINOGEN DURING HEMORRHAGIC SHOCK*†

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There are reports in the medical literature about a peculiar phenomenon affecting the blood clot called fibrinolysis. It may be described as follows: if blood is taken in a test tube without an anticoagulant and allowed to clot, it is sometimes observed that the clot disappears completely in the following minutes or hours. The blood becomes fluid again and cannot be clotted by the addition of thrombin, because the blood no longer contains fibrinogen. Fibrinolysis as defined in this paper has never been observed in the blood of normal subjects in this clinic. It has been reported to occur after the intravenous injection of peptone in dogs.[7] After callicrein injections into dogs, striking changes in the clotting of blood have been observed, which may be due to fibrinolysis.[17] In humans, it is sometimes observed following intravenous injection of typhoid vaccine[5] and is frequently seen in the rare fatal shock following intravenous injection of mercurial diuretics.[18] In a recent communication, Van S. Smith described the occurrence of fibrinolysis in the blood of patients during toxemia of pregnancy.[11]

In humans, the most extensive investigation on fibrinolysis was carried out in Russia during the development of the technique of preparing cadaver blood for transfusion.[19] It was noted by Yudin and his associates[19] that the blood of patients following *sudden* death underwent very rapid fibrinolysis, while that of patients dying as a result of a chronic disease showed no evidence of lysis of the clot. It was also observed that the blood of patients dying *suddenly* was often uncoagulable and that this was due to the absence of fibrinogen in the blood. Therefore it was found possible to store cadaver blood obtained from patients dying suddenly for transfusion purposes without the addition of an anticoagulant.

While these observations on dogs and humans are well known and generally accepted, no attempt has been made to determine the common factor, if any, which may be present in all of these conditions in which fibrinolysis occurs. From a study of the circumstances presented in the literature it seems possible that at least one of the common factors might be

* The work described in this paper was done in part under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

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the existence of peripheral vascular failure in the patients in which fibrinolysis was found. It is known that peripheral vascular failure occurs in peptone and typhoid vaccine shock as well as in that following the intravenous injection of mercurial diuretics. The cases studied by Yudin and his associates[19] were, in general, patients dying of hemorrhagic or traumatic conditions, or else from acute, non-infectious medical illnesses in which peripheral vascular failure was a part of the clinical picture.

The present communication presents evidence concerning the occurrence of fibrinolysis in the blood of patients suffering from shock due to different causes, and in dogs with hemorrhagic shock.

Observations on Humans. *Methods. For the purpose of this study, fibrinolysis is defined as a complete dissolution of the fibrin clot produced by coagulation of whole blood or plasma in the time interval of a few hours.* Reduction in the size of the clot was excluded as a criterion because of the difficulty in distinguishing between true fibrinolysis and clot retraction. Fibrinolysis occurring after 24 hours was excluded because of the possibility of bacterial contamination of the sample. The amount of fibrinolytic activity present could be roughly estimated by the speed with which complete dissolution took place.

Two methods were used in the detection of fibrinolysis. The first method consisted of taking a sample of venous or arterial blood without an anticoagulant and permitting it to coagulate in a chemically clean glass test tube, observing the time of the disappearance of the clot at 37° C. if this phenomenon occurred. The second method consisted of taking venous or arterial blood and mixing it with either sodium citrate or a mixture of potassium ammonium oxalates as an anticoagulant. The final concentration of citrate in the sample was 0.25% and that of oxalate was 0.2%. Plasma was obtained from the blood by centrifuging at 1500 to 2000 r.p.m. for 15 minutes. 0.1 ml. of the plasma was transferred to a chemically clean glass tube, diluted with 0.2 ml. of saline and recalcified with 0.1 ml. of 0.25% calcium chloride. Alternatively, clotting was produced by the addition of 0.1 ml. of a 1.25% thrombin solution. The clots so formed were observed for fibrinolysis at 37° C. The thrombin solution used was Lederle "Clotting Globulin." This material has been repeatedly shown to be devoid of fibrinolytic properties.[14] The patients studied here were admitted to the Boston City Hospital except one who was observed in another clinic. They were suffering from a variety of conditions. The usual clinical criteria for the presence of peripheral vascular failure were used, namely, rapid thready pulse, low blood pressure, cold and clammy extremities. In all, 22 patients were studied.

Results. The results of the studies on human subjects are shown in Table 1. It will be observed that of the 22 patients studied, fibrinolysis occurred in 8 individuals. With one exception, all these patients were in shock at the time fibrinolysis was observed. Three of the cases of shock were associated with extensive thermal burns and 4 with hemorrhage. The patient whose blood showed fibrinolysis and who was not in shcok was admitted in coma probably induced by a fatal dose of some barbiturate. At the time that fibrinolysis was observed in his blood, he exhibited respiratory difficulties of a serious nature consisting of slow respirations alternating with periods of complete apnea, and he was deeply cyanosed.

In 3 patients with thermal burns the observations on fibrinolysis were repeated over a considerable period of time and it was noted that the fibrinolysis which had been present during the period of shock disappeared after shock had been effectively treated.

Case Reports. All observations were carried out on venous blood except in the case of the patient L. J., in whom arterial blood was studied.

I. *Burns.* L. J. (B.C.H. 1166403), a 6 year old girl, had a flame burn over 65% of body surface, chiefly 3rd degree. Admitted in profound shock. Fibrinolysis present in diluted plasma on admission (time of dissolution 3 to 18 hours). No observation made on whole blood. Fibrinolysis absent after period of shock. Surface treatment:

triple dye. Treatment of shock: serum, blood and electrolyte solution. Temperature never exceeded 100°. Died suddenly on the 3rd day after admission, in coma and convulsions.

M. F. (B.C.H. 1163418), a 78 year old male, had a flame burn over 35% of body surface, mixed 2nd and 3rd degree. Admitted in profound shock. Fibrinolysis present on admission in diluted plasma (time of dissolution 25 minutes). No observation made on whole blood. Fibrinolysis absent after period of shock. Surface treatment: triple dye. Shock treated with plasma, blood and electrolytes. Died 18 hours after admission.

Table 1.—Fibrinolysis in Shock (in Man)

	No. of cases	Fibrinolysis
Burns:		
Shock	3	3
No shock	3	0
Hemorrhagic shock	4	4
Traumatic injury:		
Shock	1	0
No shock	4	0
"Medical" shock	7	1

H. H. (B.C.H. 1160599), a 74 year old male, had a flame burn over 75% of body surface, chiefly 3rd degree. Admitted in shock. Fibrinolysis in diluted plasma present on admission; time of dissolution 3 hours. No observation made on whole blood. Fibrinolysis absent after period of shock. Surface treatment: triple dye. Treatment of shock: plasma and electrolyte solution. Patient died 17 hours after admission.

II. *Hemorrhagic Shock.* C. H. (case contributed by Dr. G. K. Mallory), a 32 year old female, had severe postpartum hemorrhage treated with transfusion of blood and finally hysterectomy. Patient died shortly thereafter. Whole blood taken shortly before death never clotted. After spinning, the supernatant (0.1 cc.) added to fibrinogen solution (0.1 cc.) produced a clot which redissolved in 1 hour.

G. P. (B.C.H. 1131225), a 62 year old male with portal cirrhosis, was admitted in severe shock due to intractable epistaxis and hematemesis. Whole blood clotted and redissolved in 12 hours. The patient survived.

S. A. (B.C.H. 1142691), a 38 year old female, was admitted in severe shock due to massive rectal hemorrhage (etiology unknown). Diluted citrated plasma clotted on recalcification or addition of thrombin. The clot redissolved completely in 24 hours. The patient died before any attempt to treat her could be made.

G. W. (B.C.H. 1161340), a 59 year old male with portal cirrhosis, was admitted in severe shock due to bleeding esophageal varices. Treated unsuccessfully with transfusions of plasma and blood. Died shortly thereafter. Fibrinolysis observed in whole blood (rate of dissolution less than 12 hours) and in diluted plasma clotted by thrombin (rate of dissolution 25 minutes).

III. *Medical Illnesses.* M. L. (B.C.H. 1168315), a 32 year old male, was admitted in coma (probable barbiturate poisoning). Patient died 9 hours after admission. He was never in shock. Respiration was labored and interrupted by long periods of apnea. Fibrinolysis observed in diluted plasma clotted with thrombin and with calcium (rate of dissolution 1 hour) obtained from blood taken 2 hours after admission. At that time the patient was apneic. Two subsequent samples did not show fibrinolysis.

Of the 14 patients who showed no fibrinolysis, 3 were suffering from injuries due to thermal burns but were not in shock at the time when the blood samples were taken and were never in shock during their course in the hospital. Five patients had had severe traumatic injuries but in only one instance was shock present at the time of study; the state of shock was moderately severe. Six other patients were seriously ill from acute medical disorders and were all in a state of peripheral vascular failure at the time of their study.

Experimental Observations on Dogs

Methods. Nineteen (not selected) mongrel dogs, weighing between 6 and 14 kg., were used as experimental animals. Two different types of experiments were performed.

In the first type, 13 dogs (Nos. 1 to 13) were used. Eleven of them were anesthetized by the intravenous or intraperitoneal injection of 30 mg. of nembutal per kg. of body weight before the observations were made. Two animals (Nos. 6 and 13) were studied without general anesthesia; these 2 dogs received 5 mg. of morphine per kg. subcutaneously immediately before the experiment and local anesthesia with procaine at the site of the operative procedure. The blood pressure was recorded by a mercury manometer and kymograph. A No. 14 hypodermic needle was inserted in the femoral artery and the recording system was filled with saline. No anticoagulant was used. The needle was kept patent by washing it out every 5 or 10 minutes with small quantities of isotonic salt solution. Hypotension was produced by one large bleeding and maintained at the desired level by repeated small bleedings from the femoral artery. An attempt was made to maintain the blood pressure below 40 to 50 mm. of mercury; there were often fluctuations of the blood pressure since the deliberate avoidance of an anticoagulant precluded the use of automatic devices described by several authors. During the period of shock, the animal's blood pressure was so delicately balanced that it was necessary to reinject small quantities of saline or occasionally citrated blood following the removal of the necessary samples for observation. The blood samples were obtained from the femoral artery and in certain instances from the jugular vein.

In the second type of experiments, carried out on 5 dogs (Nos. 13 to 18), no general anesthesia and no morphine were used; local anesthesia by procaine or novocaine was used at the site of the operative procedure. A paraffined glass cannula was inserted in the femoral artery or deep into the jugular vein and blood was allowed to flow freely until death of the animal. This occurred between 5 and 18 minutes after the beginning of the bleeding. The blood pressure was not measured. Blood samples were obtained every 1 or 2 minutes from the flow through the paraffined cannula.

In the two series of experiments, the blood samples were taken simultaneously with and without anticoagulant. Sodium citrate in a final concentration of 0.25% was added as an anticoagulant and the plasma was removed as rapidly as possible by centrifuging. It was then either studied immediately or frozen at −30° C. and kept at that temperature. The frozen samples were thawed at 37° C. at the time of study.

The method of observing fibrinolysis and the criteria of evaluation were those described in the human investigations. In addition to the study of fibrinolysis, prothrombin time by the method of Quick[9] and fibrinogen determination by the method of Cullén and Van Slyke[2] were carried out in a certain number of instances. In all cases in which the prothrombin time was found prolonged, the measurement was repeated after addition of fibrinogen to the sample, in order to rule out an artificially prolonged prothrombin time due to deficiency of fibrinogen in the plasma sample. To rule out the possibility of the presence of an anticoagulant in the samples showing a prolonged prothrombin time, they were tested for anticoagulant as described previously.[13]

I. Sustained Shock. Results. The data are given in Table 2. Fibrinolysis was observed during the shock period in 5 of 13 experiments (Dogs 1, 3, 6, 7, 13). In no instance did fibrinolysis occur during the first 2 hours following the onset of shock. In Dog 3, simultaneous samples of venous and arterial blood were obtained from the femoral artery and the jugular vein. Fibrinolysis occurred first in the venous sample and subsequently in both the venous and arterial samples (Fig. 1). No fibrinolysis was observed in the blood of 8 animals (Dogs 2, 4, 5, 8, 9, 10, 11, 12). In these animals the duration of shock did not exceed 3 hours, with the exception of Dog 9 in which no fibrinolysis was seen, although the period of shock was 6 hours. In most instances the clot was well formed except in the samples of blood obtained from Dogs 1 and 3. In these animals at the time when fibrinolysis was present the formation of the clot was poor and after dissolution additional small fibrin clots occurred followed by resolution. The resolution of these small clots was complete in a few minutes and their presence could have been easily missed. Had this occurred the results might have been falsely interpreted as an absence of coagulation.

In no instance was fibrinolysis observed in the blood samples taken before the induction of shock or in any blood sample obtained during the first 2 hours after acute hemorrhage. The earliest appearance of fibrinolysis was $2\frac{1}{2}$ hours (Dog 6), and the latest 5 hours (Dog. 13). Once fibrinolysis had appeared it persisted in all subsequent samples until the death of the animals. Since all the animals died it was impossible to make observations on the fibrinolytic properties of the blood following recovery from hemorrhagic shock.

On 8 dogs, determinations of the prothrombin time were made simultaneously with the observations on fibrinolysis. The results are given in Table 3. The data show that the prothrombin time became somewhat more prolonged as the condition of shock persisted. The addition of fibrinogen to the plasma did not correct

TABLE 2.—FIBRINOLYSIS IN HEMORRHAGIC SHOCK (DOGS)

Occurrence of Fibrinolysis

Dog No.	Control	Hour after beginning of shock 1	2	3	4	5	6	Rate of fibrinolysis
1	0	0	0	0	+	Died	..	30 min.
2	0	0	Died					
3	0	0	0	+	Died	..	..	30 min.
4	0	0	0	Died				
5	0	0	Died					
6*	0	0	+	+	Died	..	..	60 min.
7	0	0	0	+	+	Died	..	15 hrs.
8	0	0	Died					
9	0	0	0	0	0	0	0	
10	0	0	0	Died				
11	0	0	0	0	Died			
12	0	0	0	0	Died			
13*	0	0	0	0	0	+	Died	1 hr.

* No anesthesia.

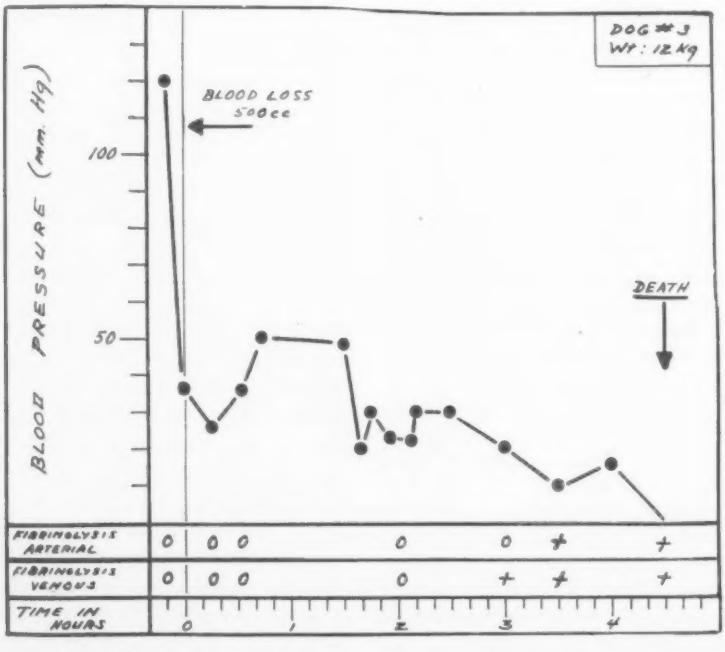

FIG. 1.—Comparison of fibrinolytic activity in venous and arterial blood in hemorrhagic shock in dog.

the prolongation of the prothrombin time, indicating that it was not due to a lack of fibrinogen in the samples of plasma. The failure of the plasma obtained during the shock phase to prolong the clotting time of normal dog or human blood was taken as an indication that there was no circulating anticoagulant produced during the shock phase.

II. Rapidly Fatal Bleeding. The data are given in Table 5. Fibrinolysis was observed in 3 instances in the last sample of blood obtained while there was still a flow of blood through the cannula (Dogs 14, 15, 17). At this time the dog was dying.

Prothrombin time and fibrinogen determinations on the samples of blood in this type of experiment showed no significant change from the control values.

TABLE 3.—PROTHROMBIN IN HEMORRHAGIC SHOCK (DOGS)

Quick Prothrombin Time (Seconds)

Dog No.	Control	Hour after beginning of shock					
		1	2	3	4	5	6
6*	13	14	17	20	Died		
7	11	12	19	24	32	Died	
8	11	12	Died				
9	11	11	12	..	..	13	17
10	12	15	19	Died			
11	12	14	17	19	23	Died	
12	13	..	..	20	26	Died	
13*	11	11	13	15	18	21	Died

* No anesthesia.

TABLE 4.—FIBRINOGEN IN HEMORRHAGIC SHOCK (DOGS)

Fibrinogen (Mg. per 100 cc. Plasma)

Dog No.	Control	Hour after beginning of shock					
		1	2	3	4	5	6
9	256	..	..	..	..	..	102
10	294	144	Died				
11	592	244	226	209	Died		
12	732	..	..	245	263	Died	
13*	346	..	150	..	132	116	

* No anesthesia.

TABLE 5.—FIBRINOLYSIS DURING RAPIDLY FATAL BLEEDING

Occurrence of Fibrinolysis

Dog No.	Control	Time from beginning of bleeding												Rate of fibrinolysis
		2	4	6	8	10	12	14	16	18	20	30	40	60	
14	0	..	..	0	..	0	..	..	+	Died	..	..	..	..	24 hrs.
15	0	0	0	+	Died	..	..	..	..	..	..	..	..	..	3 hrs.
16	0	0	0	0	Died										
17	0	0	0	+	Died	..	..	..	..	..	..	..	..	..	3 hrs.
18	0	..	0	..	0	..	0	..	0	Died	..	..	..	..	
19	0	..	0	..	..	..	0	..	..	..	..	0	0	Died	

On Dogs 9, 10, 11, 12, 13, determinations of the fibrinogen level in the plasma were carried out simultaneously with prothrombin determinations and observation on fibrinolysin. In all 5 there was a marked and progressive fall of the fibrinogen, paralleling roughly the fall in prothrombin. In all cases, the fall in these constituents preceded the appearance of detectable fibrinolysis (Table 4).

Discussion. Observations in this laboratory on many hundreds of samples of blood on normal individuals have shown that fibrinolysis never occurs in whole blood or plasma clotted by recalcification or on the addition of thrombin, within an observation period of 24 hours. Therefore, it would appear that the fibrinolysis re-

ported here cannot be accounted for on the basis of bacterial contamination or other artifacts, since in no instance was an observation made for longer than 24 hours and the actual time required for the complete digestion of the clot was much shorter than this time interval.

The present observations in humans strongly suggest some interrelation between the presence of peripheral vascular failure due to burn or hemorrhage and the presence of fibrinolysis. All the patients whose blood showed fibrinolytic activity were in shock, and, in two of them, the fibrinolysis disappeared on recovering from the peripheral vascular collapse. In contrast, none of the six patients with serious medical illnesses, who were in peripheral vascular failure, showed fibrinolysis. The 1 patient who was not in shock showed definite evidence of marked anoxia due to anoxemia. Since it is highly probable that peripheral vascular failure is associated with anoxia, it is possible that the precipitating cause of the existence of fibrinolysis is the existence of a prolonged anoxic state. It would appear that, in the small group of patients studied here, fibrinolysis was most frequently associated with shock produced by hemorrhage and burns, and, less frequently, with peripheral vascular collapse associated with medical illnesses. Further observations are needed before this point can be clearly demonstrated.

Generally speaking the experimental evidence obtained on dogs in hemorrhagic shock as reported here is in agreement with the results of the observations on the patients in hemorrhagic shock. In the first series of experiments, the occurrence of fibrinolysis was observed in 5 dogs, 2 of which were not anesthetized (Nos. 6 and 13). However, in these 5 animals, fibrinolysis was never observed earlier than 2 hours after the onset of shock. All but 1 (No. 9) of the 8 dogs in which fibrinolysis was not observed died before the 4th hour after the onset of shock, 3 of them (Nos. 2, 5, 8) dying quite early, and it is conceivable that the rapid death may explain the absence of fibrinolysis. It should be pointed out that by the method used in this work, complete disappearance of the clot is taken as evidence of fibrinolysis. It is entirely possible that fibrinolysis may be present before it becomes intense enough to bring about complete dissolution of the clot and that more sensitive methods of detection would demonstrate its occurrence before complete dissolution occurs. However, the present data would indicate that fibrinolysis is produced by the presence of the shock state rather than preceding it.

In the second series of experiments, fibrinolysis was observed in 3 of 5 dogs and, in all cases, it appeared only in the last sample of blood, obtained shortly before death. In this series of experiments, the time of appearance of fibrinolysis, counted from the beginning of the bleeding, was quite in contrast with that seen in the first series. The difference in the time relationship may be due to the more rapid and abrupt type of disturbance produced in the second series of experiments as compared to the first ones. The second type of experiments was performed precisely in order to bring out this point.

From the data reported here the prolongation of the prothrombin time observed in 8 experiments on dogs seemed to be a constant occurrence when the state of shock produced by hemorrhage was of sufficient duration and intensity. It cannot be explained by the presence of an anticoagulant. Also it was not due to a deficiency of fibrinogen in the plasma since it was not corrected by the addition of fibrinogen to the plasma. It seems therefore that the prolongation of the prothrombin time in these experiments was actually due to hypoprothrombinemia. As far as we know, this is the first time that the occurrence of hypoprothrombinemia has been reported in hemorrhagic shock. Theoretically, hypoprothrombinemia can be explained on the basis of vitamin K deficiency, liver dysfunction, intravascular coagulation or destruction of the prothrombin by enzymatic digestion. No data

are available to indicate the possible influence of hemodilution, which occurs in hemorrhagic shock, in bringing down the prothrombin concentration in the blood of the dogs studied here, but it does not seem probable that hemodilution alone could explain changes in the prothrombin as marked as reported here. Vitamin K deficiency usually does not manifest itself in a period of a few hours although it is conceivable that it might do so during shock, in which state an increased demand for other vitamins has been observed.[20] Liver dysfunction is a conspicuous manifestation of hemorrhagic and traumatic shock and liver dysfunction could constitute the cause of the hypoprothrombinemia reported here.[1,16] Final proof that such is the case would seem difficult to obtain in view of the fact that hepatectomy is by itself a very serious operative procedure which may produce shock and since hemorrhagic shock alone is able to produce hypoprothrombinemia, it would seem that no conclusion can be reached from a comparison of the rates of disappearance of prothrombin in hepatectomized and shocked animals.

The intravenous injection of certain proteolytic enzymes is known to cause a reduction of the prothrombin level, either by promoting intravascular coagulation with the consumption of the plasma prothrombin[13] or by their direct action of digesting prothrombin *in vivo*.[15] In both cases, the reduction in prothrombin is paralleled by a decrease of the fibrinogen level of the plasma. Fibrinogen determinations on 5 dogs carried out in 5 experiments reported here showed a significant reduction in the level of fibrinogen concomitant with the fall in prothrombin. There is therefore a possibility that the hypoprothrombinemia and fibrinogenopenia in hemorrhagic shock might be due to the fibrinolytic activity. The data obtained so far do not offer any evidence as to whether the decrease in prothrombin and fibrinogen is due to such a direct digestive action or due to a slow intravascular coagulation.

It would seem that the hypoprothrombinemia and fibrinogenopenia observed in hemorrhagic shock, as reported here, may be of importance in the evaluation of the therapy of shock in humans. It may indicate that the usefulness and indications of blood and plasma substitutes devoid of prothrombin and fibrinogen should be reconsidered if shock in humans results in similar reduction in prothrombin and fibrinogen. If such were the case, it is probable that any fluid used in the treatment of shock, in addition to fulfilling the well known requirements, should be able to replace the deficient constituents. In that respect, whole blood and those preparations of plasma, containing normal amounts of prothrombin and fibrinogen, have no adequate substitutes.

The absence of fibrinolysis in certain cases of peripheral vascular failure in humans can be explained either by the absolute absence of fibrinolysis or, equally well, by a failure on our part to obtain a blood sample at the time when fibrinolysis was present. At present nothing is known about the exact conditions and the time relations under which fibrinolysis appears following human peripheral vascular failure. From the experimental data it would appear that fibrinolysis as determined by the present method is not observable at all times during the shock state. Furthermore, the transient nature of the phenomenon is obvious for it completely disappears when the shock present is adequately treated. The transient nature of the phenomenon could well explain our failure to observe it in all cases of shock. It is possible that a more sensitive method than the one used here would be able to detect fibrinolysis in a greater number of cases.

Final proof is not available to demonstrate that the phenomenon of fibrinolysis is due to proteolysis. However, it has been previously demonstrated that fibrinolysis can be produced by artificial means in normal plasma, as for example, by shaking the plasma with chloroform. Under these circumstances the fibrinolytic activity is accompanied by or associated with the

production of proteolytic enzyme.[14] Recently, it has been shown that fibrinolysis produced by streptococcus toxin is probably enzymatic in nature.[6] Therefore, reasoning by analogy it is probable that the fibrinolysis reported in this communication may likewise be due to proteolysis.

One may speculate on an origin of the fibrinolytic enzyme. It could originate from the plasma itself due to an activation of an inactive precursor of a plasma enzyme,[12] or it could arise from cellular elements of damaged tissue. Present evidence does not permit a definite conclusion on this point. The latter probability is suggested by the fact that in one experiment the fibrinolytic activity was found to be present in venous blood a long time before it appeared in arterial blood. This observation could be interpreted as meaning that there was a release of intracellular elements in the blood stream.

It has been demonstrated[10,13,15] that certain proteolytic enzymes are toxic when injected intravenously. In fact they are able to produce a state of shock in experimental animals. This type of shock is associated with changes in the blood coagulation mechanism, some of which are not unlike those, reported here, following hemorrhagic shock in dogs. Therefore, if fibrinolysis is caused by a proteolytic enzyme, it is probable that the presence of such an enzyme in the blood stream during shock might well constitute a sustaining and aggravating factor. Its relation to shock as an initiating factor is not at present clear.

Summary. 1. The spontaneous dissolution of a whole blood clot or one of diluted plasma is called fibrinolysis. The occurence of fibrinolysis was observed in 8 out of 22 severely ill patients.

2. Of the 8 patients whose blood showed fibrinolysis, 4 were in severe hemorrhagic shock, 3 in severe shock due to extensive flame burns, 1 was poisoned probably by some barbiturate.

3. In hemorrhagic shock produced experimentally in 13 dogs, fibrinolysis was observed in 5 instances. In 6 dogs with rapid fatal bleeding fibrinolysis occurred three times.

4. In hemorrhagic shock in dogs, there was a marked and progressive fall in the levels of prothrombin and fibrinogen in the plasma.

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OBSERVATIONS ON THE SPECIFICITY AND CLINICAL USE OF DIROFILARIA IMMITIS ANTIGEN IN THE DIAGNOSIS OF HUMAN FILARIASIS (WUCHERERIA BANCROFTI)

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The incidence of filariasis among American troops located in endemic areas in the South Pacific has increased the importance of this disease, and has brought new problems to the attention of the medical department. Outstanding is the need for further laboratory aids in the diagnosis of early human filariasis. The findings of lymphangitis, lymphadenopathy, epididymo-funiculitis, orchitis, and scrotal swelling, associated with service in known filarial endemic areas may be regarded as good clinical evidence for filariasis. Nevertheless, it is necessary to rule out other etiologic agents for the above signs and symptoms and to have laboratory confirmation of the disease.

It has been pointed out by King[6] that a positive diagnosis for filariasis may be made by three methods: microscopic demonstration of adult filaria in biopsy specimens, demonstration of microfilariæ in the blood stream, and the demonstration of calcified worms by Roentgen ray technique.[12] These methods depend on the finding of either the larval or adult worm in the human host. Thus far only the biopsy procedures[10,14,15,17] have been reported successful. Although microfilariæ have been found in abundance in the peripheral blood of infected natives, the blood stream of American soldiers has been reported persistently negative to the present time. Roentgen ray examinations have not been of diagnostic value.

Although positive evidence from biopsy examination is definite and incontrovertible, this procedure contains certain disadvantages for routine usage. It is time consuming, requires surgical intervention, and furthermore a negative biopsy may require removal of an additional gland for further study. Finally, the biopsy procedure is not applicable to an investigation of filariasis in a group survey. Consequently, it was decided to study the possibility of using a test involving an increased sensitivity of the individual. Experimental work has already been reported on the intradermal response and serologic tests with an antigen prepared from the dog heart worm, *Dirofilaria immitis*.

In 1930, Taliaferro and Hoffman[16] reported the use of a 1:200 dilution of a saline extract of *Dirofilaria immitis* antigen in cutaneous tests. Fairley[4,5] used a dilution of 1:200 and 1:1000 of a saline extract of *Dirofilaria immitis* for both intradermal and complement fixation tests. He injected 0.25 cc. and obtained positive reactions in many suspected cases. Further work on the complement fixation reaction with the Dirofilaria antigen was carried out by Lloyd and Chandra.[8] In a series of 89 cases showing clinical symptoms of filariasis, 26% gave a positive response. In a series of 15 cases with helminthic infections other than *Wuchereria bancrofti*, 3 positive results were obtained. In all 3 cases, the parasitic worm was *Dracunculus medinensis*.

In the more recent studies, Dickson, Huntington and Eichold[3] investigated the intradermal response of Navy personnel stationed on Samoa. Using an extract of *Dirofilaria immitis* and working with two groups, the authors obtained a positive reaction in 83.1% of a group of 137 patients showing clinical filariasis. In a second control group of 128 individuals who showed no symptoms and had been

4 weeks or less in the endemic area, a positive reaction was obtained in 4.7%. These authors further state that in one instance an adult filarial worm was found in a patient with a negative skin test, indicating that desensitization may have taken place. Comparative tests with an extract of *Ascaris lumbricoides* revealed a certain degree of cross-reactivity. Since the authors give no information concerning the dosage and dilution, it is difficult to draw any conclusions.

In 1944, Michael[10] reported the results of skin tests with Dirofilaria antigen on 307 patients with filariasis. He obtained a positive response in 87.3%. King[6] using a 1:1000 dilution of Dirofilaria antigen obtained a positive response in 90.8%.

In an attempt to arrive at a dilution of the Dirofilaria antigen which would be specific for filariasis, Bozicevich and Hutter[1] injected 0.01 cc. intradermally using a number of dilutions. They obtained positive results in 25 patients with a dilution of 1:8000, and were able to conclude that this dilution would screen out false positive reactions due to allergies and malaria. Complement fixation studies were negative.

The possibility of using the microfilaria of *Wuchereria bancrofti* in preparation of an antigen was investigated by Oliver-Gonzalez and Bercowitz.[13] These authors carried out precipitin tests and obtained 2 positive reactions from 26 patients with microfilariæ in the blood and 3 positive reactions from 14 patients with clinical filariasis.

Additional work has been reported on the use of an extract prepared from *Litomosoides carini* (Culbertson, Rose and Demarest).[2] Thus far there is no evidence that this extract is superior to one prepared from *Dirofilaria immitis*.

In view of the lack of sufficient data on the problem of cross-reactions in patients with intestinal helminths and on the specificity of this antigen, it was thought worth while to investigate these problems. We have attempted, by a titration of the Dirofilaria antigen, to determine first, the dilution at which false positives due to intestinal helminths may be ruled out and, second, the sensitivity of patients with filariasis to the antigen. In addition it was possible for us to compare results obtained from both biopsies of lymph nodes and skin tests on the same patients.

Material and Methods. In the early stages of this investigation, the antigen was prepared according to the method of Huntington as reported by Michael.[11] Certain minor modifications were made during the investigation and the procedure was standardized in the following manner. Dogs were sacrificed by an intravenous injection of magnesium sulfate and their hearts removed. An incision was made immediately into the right ventricle and auricle and the adult *Dirofilaria immitis* worms were removed and placed in an evaporating dish containing physiologic saline. They were carefully cleaned of any clotted blood and placed in running water overnight. On the following morning the worms were washed in several changes of distilled water and then treated with three changes of acetone, following which they were placed in an incubator (37° C.) to dry. After 12 hrs., the worms were thoroughly dried. They were then ground up in a mortar and pestle, and the powder kept, well corked, in a refrigerator.

The extract was prepared by weighing out the powder and making a 1% suspension in physiologic saline. The extraction was allowed to proceed for 2 hrs. at 37° C. with constant stirring. The extract was then sterilized by filtration through a Seitz filter and phenol added to make a 0.3% concentration. From this stock extract (1:100) the following series of dilutions were made for use in the titration of the antigen: 1:200, 1:2000, 1:4000, 1:8000 and 1:16,000.

It has been an observation of this laboratory that the extracted material will lose its potency. Consequently the dried powder was kept as the stock source and new dilutions were made every month. The lack of knowledge as to the chemical nature of the antigenic substance made it necessary to check the potency of the extract very carefully. In an attempt to refilter a contaminated batch of the extract, a decided loss in potency was noted. This observation

has since been reported by King[6] who went on to postulate that we may not be dealing with a true solution and "that perhaps part of the antigenic fraction is held in suspension in the saline solution."

In drying the adult worms after treatment with acetone, it is necessary to watch the temperature. A loss in potency was obtained when the temperature rose above 37° C.

For a control in the intradermal tests, a fragment of dog heart was removed and treated identically as the antigen. This was made up to a dilution of 1:2000 and stored with the antigen in the refrigerator.

In running the skin tests, a volume of 0.05 ml. was injected intradermally on the volar surface of the arm. One arm received an injection of the control material and antigen dilutions of 1:200 and 1:2000. The other arm received the three remaining dilutions of 1:4000, 1:8000, and 1:16,000. At first the reaction was read at 30 min., 1 hr., and 24 hrs. after injection. The 1 hr. read- was soon dropped in favor of a single 30 min. reading, at which time the height of the reaction occurs. In all instances, the 24 hr. reaction was observed and taken into consideration. Occasionally, the arm that received the 1:200 and 1:2000 dilution of Dicrofilaria antigen revealed an elephantoid reaction at the 24 hr. period.

In determining a positive response, the size of the wheal, diameter of the erythema, and presence of pseudopodia were taken into consideration. A definite increase in wheal size over the control plus an erythema measuring 2 cm. or more was considered positive.

Stools were examined on all patients by the zinc sulfate flotation method and by direct smear. All patients had a minimum of 2 examinations and many had 5 examinations.

Results. The first problem that interested us was to investigate the sensitivity of patients with intestinal helminthiasis to intradermal injections of *Dirofilaria immitis* antigen. A series of 65 patients harboring hookworm, *Strongyloides stercoralis*, *Ascaris lumbricoides*, *Enterobius vermicularis* and *Hymenolepis nana*, all free of clinical filariasis, were injected with the antigen. With one exception, no positive reaction was obtained with a dilution higher than 1:2000 (Table 1).

The one exception was a patient with herpes zoster in addition to ancylostomiasis. In view of a positive response with the control injection, it was felt that this patient may well be disregarded.

Wright and Murdock[18] obtained cross-reactions with *Dirofilaria immitis* antigen in patients with a dilution of 1:4000. However these authors injected a total volume of 0.1 cc. which is double the volume used in the present study. Consequently the contradiction in results on the cross-reaction is not a real one.

Of 91 patients with clinical symptoms of filariasis injected with the various dilutions of the Dirofilaria antigen (Table 2), 83 (91%) gave a positive response to at least one of the dilutions. In a controlled group of 18 individuals with no history of service in an area endemic for filariasis and free of clinical symptoms and signs, 11 gave a negative response to a 1:200 dilution of the antigen, 5 gave a positive response to a 1:200 dilution of the antigen, and 2 gave a positive response to a dilution of 1:2000 of the antigen. No response was obtained at higher titers. Considering the data from the cases with intestinal helminths and from the control cases, it appears that a positive response to a dilution of 1:4000 and higher is indicative of filarial infection. Using this as a basis for the interpretation of our results, we obtained a positive response with the Dirofilaria skin test in 78% of the cases.

In an attempt to determine the specificity of the intradermal test with Dirofilaria antigen, we were able to compare the results of lymph node biopsy with the results from skin tests (Table 3). In a group of 53 patients, 74% gave a positive skin test to a dilution of 1:4000 to 1:16,000 of the Dirofilaria antigen. Biopsies were positive for filariasis in 60% of these cases. It is of interest to note that in several instances more than one biopsy had to be performed on a single patient before a positive gland was obtained. It is possible that further biopsies on the

TABLE 1.—CROSS-REACTIONS OBTAINED WITH DIROFILARIA ANTIGEN SKIN TEST AND HEMATOLOGIC FINDINGS IN 63 PATIENTS WITH INTESTINAL HELMINTHIASIS

Intestinal helminths	No. cases	Dilution giving pos. skin test with Dirofilaria antigen	RBC (mill./ c.mm.)	WBC (thous./ c.mm.)	Hb. (%)	Lympho-cytes (%)	Eosinophils (%) Av.	Eosinophils (%) Range
Hookworm	11	None	4.4	6.4	91	33	21	7-43
	14	1:200	4.5	9.1	92	34	18	6-31
	12	1:2000	4.5	9.3	96	26	28	2-69
	1	*1:8000	4.7	7.5	92	30	11	
Total	38							
S. stercoralis	5	1:200	4.5	7.2	94	22	14	5-26
	7	1:2000	4.8	8.8	96	30	19	8-23
Total	12							
A. lumbricoides	4	1:200	4.5	9.6	90	29	21	10-29
	2	1:2000	4.7	10.2	92	31	17	12-22
Total	6							
E. vermicularis	2	None	4.2	7.4	88	28	3	2- 4
H. nana	2	None	4.9	6.1	98	36	5	4- 6
	3	1:200	4.6	7.8	95	38	6	4- 8
Total	5							

* The intradermal response to the control solution was also positive. (Patient had herpes zoster in addition to ancylostomiasis.)

TABLE 2.—TITRATION OF THE DIROFILARIA ANTIGEN INJECTED INTRADERMALLY IN PATIENTS WITH CLINICAL FILARIASIS AND THE HEMATOLOGIC FINDINGS

No. cases	Dilution giving pos. skin test with Dirofilaria antigen	Interpre-tation of skin test	RBC (mill./ c.mm.)	WBC (thous./ c.mm.)	Hb. (%)	Neutro-phils (%)	Lympho-cytes (%)	Eosinophils (%) Av.	Eosinophils (%) Range	No. patients showing 6% or more eos.
				CLINICAL FILARIASIS						
8	None	Neg.	4.5	9.8	93	64	28	4	0- 8	1
10	1:200	Neg.	4.5	8.8	95	56	34	4	1-10	1
2	1:2000	Neg.	4.7	9.7	97	50	43	3	2- 4	None
20*										
17	1:4000	Pos.	4.5	8.8	94	59	30	7	2-17	12
25	1:8000	Pos.	4.5	8.8	95	58	30	7	0-29	10
29	1:16000	Pos.	4.5	8.9	93	52	38	8	0-40	7
71†										
				CONTROLS—NO CLINICAL FILARIASIS						
11	None	Neg.	4.6	9.0	98	57	35	4	1- 7	1
5	1:200	Neg.	4.5	7.8	97	58	35	3	1- 5	None
2	1:2000	Neg.	4.8	7.2	99	62	29	4	3- 5	None
18										

* Intestinal helminths present in 2 patients.
† Intestinal helminths present in 11 patients.

TABLE 3.—COMPARISON OF RESULTS OBTAINED FROM INTRADERMAL TESTS WITH DIROFILARIA ANTIGEN AND BIOPSY OF LYMPH NODES ON 53 PATIENTS

Test	No.	%
Biopsy—Positive	32	60
Negative	21	40
Skin test*—Positive	39	74
Negative	14	26
Biopsy negative and skin test positive	10	18
Biopsy positive and skin test negative	3	6

* Only reactions to 1:4000 or higher dilutions of the antigen were interpreted as positive.

10 cases with a negative biopsy and positive skin test would bring the two figures into closer agreement.

In 3 cases (6%), a positive biopsy was obtained with a negative skin test. This lack of skin sensitization has also been noted by Dickson, Huntington and Eichold[3] and appears to be a true phenomenon and not due to a loss in potency of the extract.

Using the dilutions of 1:4000 and 1:16,000, a survey was made of 55 soldiers at their company aid station. All had been exposed to filariasis, some showing a clinical picture of enlarged nodes, and others clinically free. In this group, 71% gave a positive skin test to the Dirofilaria antigen.

Complete blood counts were carried out on all the patients with filariasis (Table 2). No marked deviations from the normal average were noted in the red blood cell count, hemoglobin, neutrophils or lymphocytes. While the average white blood cell count for all the filarial patients was normal, 25% showed an elevation to 10,000 or slightly higher of white blood cells per c.mm.

The eosinophils were elevated in 34% of the entire group of 91 patients showing clinical filariasis. However if we consider only the group with a positive skin test of 1:4000 or greater, 40% showed an elevated eosinophilia. In this latter group, intestinal helminths were found in 15% of the patients.

A diligent search of all cases for microfilaria in the circulating blood failed to give any positive results, even though adult worms containing microfilaria were found by biopsy. All blood was examined by both the fresh smear and by the Knott concentration method.[7] In the first method a drop of blood was mixed with a drop of saline and the preparation examined for motile larvæ. In the second procedure, 1 cc. of blood was laked with 10 cc. of 2% formalin. The sediment was smeared out and stained with Giemsa or methylene blue and eosin. Though the variety of *Wuchereria bancrofti* in this area of the South Pacific has a non-periodic larva (Manson-Bahr),[9] concentrations were made at different intervals of a 24 hour period. In one instance a patient, shown on biopsy to have an adult worm containing microfilariæ in its uterus (Rifkin),[15] have been examined every 2 hours. In several cases, 10 to 20 ml. of blood were removed for concentration, yet negative results were obtained.

Summary. 1. The use of a dilution of 1:4000 of the *Dirofilaria immitis* antigen rules out false positive reactions due to intestinal helminths.

2. In a series of 91 patients with clinical filariasis, 78% gave a positive skin test with a titer of 1:4000 or higher of the Dirofilaria antigen.

3. In a group of 53 patients, a positive biopsy was obtained in 60% of the cases and a positive skin test in 74% of the cases.

4. Three patients with a positive biopsy gave negative skin tests.

5. Of a group of 55 soldiers who had been exposed to filariasis (field survey), 71% gave a positive response to a titer of 1:4000 to 1:16,000 of the Dirofilaria antigen.

6. An increased eosinophil count was found in 40% of the patients with a positive Dirofilaria skin test of 1:4000 or greater.

7. No microfilariæ were found in the peripheral blood though many patients were shown to have adult worms or worm foci in their lymph nodes.

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THE TREATMENT OF BACILLARY DYSENTERY IN CHINESE SOLDIERS WITH SULFAGUANIDINE AND SULFADIAZINE

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The opportunity to make controlled observations of the efficacy of sulfaguanidine and sulfadiazine in the treatment of acute bacillary dysentery has recently presented itself to us. In an Army General Hospital in northeastern India caring for Chinese and American troops we have observed many hundreds of cases within the past year. It early became apparent that we were dealing with a relatively benign form of the disease with a uniformly favorable outcome. Under these circumstances it seemed both justifiable and important to utilize the opportunity to determine to what extent sulfonamide therapy shortened the course of the disease or otherwise favorably influenced its course. The present communication describes the results of such an investigation, carried out in the 7 month period from June through December 1943, in which the results of treatment were compared in 334 Chinese patients with bacillary dysentery, one-third of whom received no medication except a placebo, one-third received sulfaguanidine and one-third sulfadiazine.

Method of Study. A tentative diagnosis of bacillary dysentery was made on the history of the sudden onset of abdominal pain, fever and the frequent passage of bloody, mucous stools. On admission to a dysentery ward each patient was immediately placed, without any selection, into 1 of 3 groups, those to receive (*a*) sulfaguanidine, (*b*) sulfadiazine and (*c*) a placebo. After the usual history and physical examination were completed a notation was made as to the duration of the disease prior to admission, and an impression was recorded of whether the patient was slightly, moderately or severely ill. Either on the day of admission or on the following morning a stool specimen was obtained for gross and microscopic examination and for culture. In making the stool cultures, selected material was emulsified in physiologic saline, and 2 or occasionally 3 surface plates were inoculated. The media employed varied according to availability, and included eosin-methylene blue agar, Leifson's desoxycholate-citrate agar, "Bacto-SS" agar and Endo's agar. At least 2 of these media were used for each specimen. The eosin-methylene blue and the desoxy-cholate-citrate agar proved most satisfactory. Suspicious colonies were isolated after 18 to 36 hours and identified by cultural characteristics. During the latter half of the study when antisera were available the identity of all strains was confirmed by agglutination against specific antisera, using a microscopic agglutination test with living organisms.

Blood counts were routinely made, and the leukocyte count was repeated every 2nd day if it exceeded 8000 per c.mm. Patients were weighed on admission and on discharge. Medication was begun on the 1st or 2nd hospital day, on the following dosage schedule, either sulfaguanidine, 3.5 gm. every 4 hours, or sulfadiazine in an initial dose of 3 gm., followed by 1 gm. every 4 hours, or a placebo consisting of lactose capsules or colored, flavored water, given 3 times daily. No other drugs were employed. The medication was continued for a variable period of time depending upon the subsequent course of the disease. A strenuous effort was made to insure that each patient drank at least 3 liters of fluid daily. All patients consumed the same diet and received the same ward care by a fixed personnel. Daily observation of the number of stools passed, their consistency (whether or not they contained blood or mucus) was made by the patient and tabulated on the clinical record. We were forced to rely on the patient's own stool counts.

This was necessitated by the large number of cases handled at the same time, and by the limited size of the ward staff. Inaccuracies doubtless occurred, but in general we were impressed by the meticulous accuracy with which the Chinese patients enumerated the daily number of stools passed. Whenever doubt existed as to the accuracy of the count the ward staff inspected all stools passed in a 24 hour period. If the observed number was greatly at variance with previous counts the case was excluded from the study. Whatever the inaccuracies they were presumably equally distributed in the 3 groups, and in a series as large as this could scarcely have altered the results significantly. The patients were discharged from the hospital at the earliest moment they were considered able to resume duty. In those instances where hospitalization was prolonged for other reasons a notation was made of the point at which the dysentery was no longer considered the cause of disability.

In the 4th group of patients, 50 in number, treatment was not begun immediately for reasons discussed later. They presented a subacute form of the disease and were treated with sulfaguanidine or sulfadiazine, in the dosage indicated above, after a control period without medication.

All patients admitted with the presenting symptom of severe diarrhea or dysentery obviously did not have true bacillary dysentery. The 2 commonest diseases with which it was easily confused were acute amebic dysentery and the dysenteric form of malaria. Cases of simple diarrhea, without blood or mucus in the stools, which subsided within 48 to 72 hours were occasionally assigned to the dysentery wards. All patients falling into these 3 groups were excluded from the study as soon as the proper diagnosis was established.

Results. Included in the study were 334 cases. In 25% the clinical diagnosis of bacillary dysentery was confirmed by positive stool cultures, in the remaining 75% the diagnosis was made on clinical grounds alone. [It is well known that in many cases of bacillary dysentery the bacteria may not be recoverable after the first few days.—ED.] The latter group were in every respect similar to those in which the diagnosis was bacteriologically verified, and other possible causes of dysentery were excluded. No doubt existed in our minds that these patients were in fact suffering from true bacillary dysentery in spite of a single negative stool examination. Of the 334 cases 284 had an acute form of the disease and were divided into 3 groups, for immediate treatment as follows: 105 were controls receiving only a placebo, 75 received sulfaguanidine and 104 sulfadiazine. In each of these 3 groups the number of cases with positive stool cultures was almost identical. A smaller group of 50 received one or the other drug later in the course of the disease, after a control period without medication. In Table 1 are data, excluding the latter 50, showing the age of the patients, the duration and severity of the illness, the admission blood studies and temperature readings, and the incidence of intestinal helminths, which were predominantly ascaris, hookworm and trichuris. Examination of the figures confirms, we believe, our clinical impression that the 3 groups of patients were comparable in every respect. Indeed, this would be anticipated from the fact that the patients were assigned to the 3 groups in rotation, without any selection whatever.

Chart 1 contains a graphic representation of the average daily stool counts in each of the 3 groups. The control group, with an initial average stool count of 15 per 24 hours, appears to have had a slightly more severe form of infection. Even so, the rate of subsidence of the dysentery was entirely comparable to that in the treated cases, and by the end of 1 week the average stool counts in all 3 groups were identical. It is clear that the sulfonamides did not materially reduce the frequency of the stools.

In Table 2 are data which indicate that the febrile phase of the disease was not influenced by the administration of a sulfonamide nor was the period of hospitalization shortened. All groups gained equally in weight. It is our distinct clinical im-

pression that in the untreated cases symptoms and physical signs subsided as rapidly as in those who received specific medication.

Stool culture yielded a variety of dysentery organisms of which the most frequently encountered were *Sh. paradysenteriæ-Flexner*, *Sh. dysenteriæ* and *Sh. paradysenteriæ-Hiss*. Of the positive cultures 85% fell into 1 of these 3 groups. The incidence of the various types of organism in the control and treated series was roughly comparable (Table 3). It will be observed from Table 1 that the percentage of positive stool cultures was relatively low, from 25 to 34%. This is probably to be expected in view of the fact that only a single culture was obtained, and this, on the average, 6 days after the onset of symptoms. It was of interest to determine whether the bacteriologically proved cases were more susceptible to the sulfonamides than those in which the diagnosis was based on clinical grounds alone. In Chart 2 is a representation of the average daily stool counts in the treated and untreated patients with positive stool cultures. Their rate of recovery, as judged by this criterion, appears to have been equally rapid, and entirely comparable to the group as a whole.

In Chart 3 are data on 50 miscellaneous cases which were not, for one reason or another, acceptable in the larger groups just described. They represent, in part, cases in which treatment was delayed either because of uncertainty in diagnosis or the presence of complicating diseases such as malaria. Some were transferred to the dysentery wards late in the disease, others had received previous medication, still others had relapsed after an initial improvement with or without treatment. This group, on the average, was admitted

TABLE 1.—CLINICAL AND BLOOD DATA IN CONTROLS AND THE SULFONAMIDE TREATED GROUPS

	Control group	Sulfaguanidine group	Sulfadiazine group
Av. age (yrs.)	27	29	27
Av. duration of symptoms prior to admission (days)	5.2	5.0	5.4
Severity of illness:			
1. Slightly	56%	53%	69%
2. Moderately	42%	41%	29%
3. Severely	2%	6%	2%
Av. temperature on admission	99.4°	98.6°	98.4°
Av. maximum temperature during hospitalization	100.4°	100.4°	100°
Positive stool cultures	30%	34%	24%
Av. WBC count on admission	8400	8400	7600
Av. Hb. on admission (gm.)	14.6	13.8	14.0
Intestinal parasitism	25%	25%	31%

TABLE 2.—DURATION OF FEVER, HOSPITALIZATION AND MEDICATION AND GAIN IN WEIGHT IN 3 GROUPS

	Control group	Sulfaguanidine group	Sulfadiazine group
Av. febrile hospital days	2	2	2
Av. period of hospitalization (days)	12	13	12
Av. weight gain (pounds)	5	6	5
Av. days of medication	0	9	6

TABLE 3.—TREATMENT GROUPS ACCORDING TO DIFFERENT TYPES OF SHIGELLA

	Control group	Sulfaguanidine group	Sulfadiazine group
Total number of cases with positive stool cultures	24	23	22
Organism:			
Sh. paradysenteriæ Flexner	14	13	8
Sh. dysenteriæ	5	5	3
Sh. paradysenteriæ Hiss	2	2	7
Sh. paradysenteriæ Sonne	1	2	2
Sh. paradysenteriæ Strong	2	1	1
Sh. dispar	0	0	1

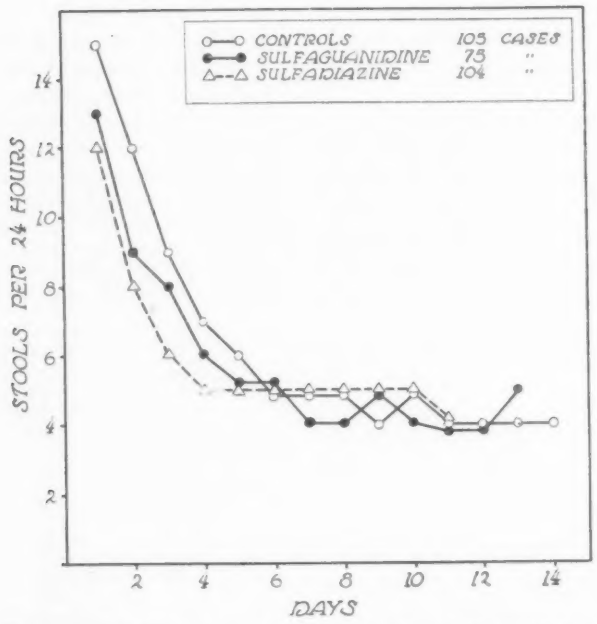

CHART 1.—The average daily stool counts in the control and sulfonamide treated patients.

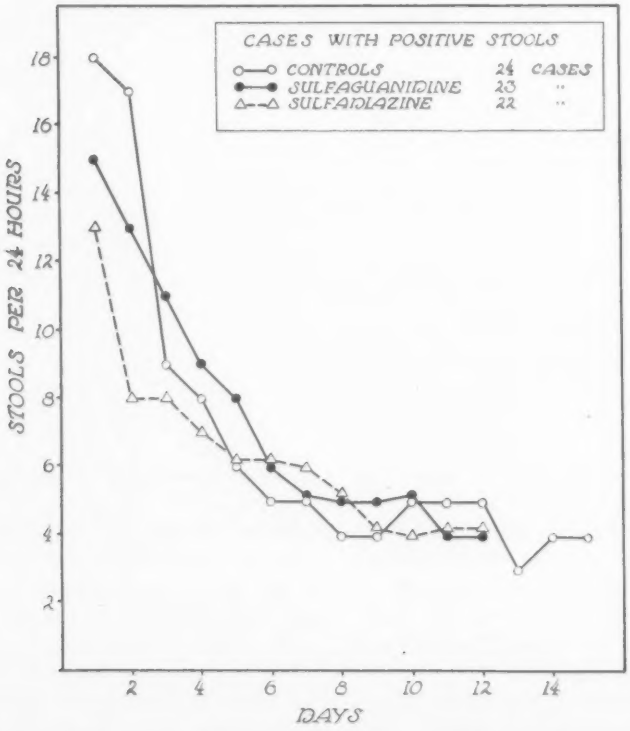

CHART 2.—The average daily stool counts in the control and sulfonamide treated patients with positive stool cultures.

to the hospital on the 8th day of the disease, only 20% had positive stool cultures, and treatment with a sulfonamide was begun on the 18th day of the disease, and continued for 8 days. While the group is made up of subacute, chronic and atypical forms of the disease rather than the classical acute type of bacillary dysentery, the results of therapy seem worth recording since such cases were frequently encountered. It would appear that both drugs, especially sulfaguanidine, reduced the stool counts somewhat, but the effect was not an impressive one.

while in 1 urine flow was reëstablished spontaneously after the liberal administration of parenteral fluids.

Mortality. No deaths occurred in the cases reported here. Only 1 case has terminated fatally in our entire experience. This was a patient with a choleraic form of the disease who died very shortly after admission and who was thought to have, in addition, typhus fever.

Discussion. A critical examination of our data has failed to provide us with evidence that the clinical course of acute bacillary dysentery was significantly affected by the administration of either sulfaguanidine or sulfadiazine. They produced no discernible amelioration of symptoms, nor subsidence of positive physical findings. The progressive decrease in the number of daily bowel movements appeared to be essentially equal in both treated and untreated groups. The febrile phase of the disease lasted on the average only 2 days after hospitalization regardless of the method of treatment. The duration of illness, an all-important military consideration, was not reduced by the administration of a sulfonamide.

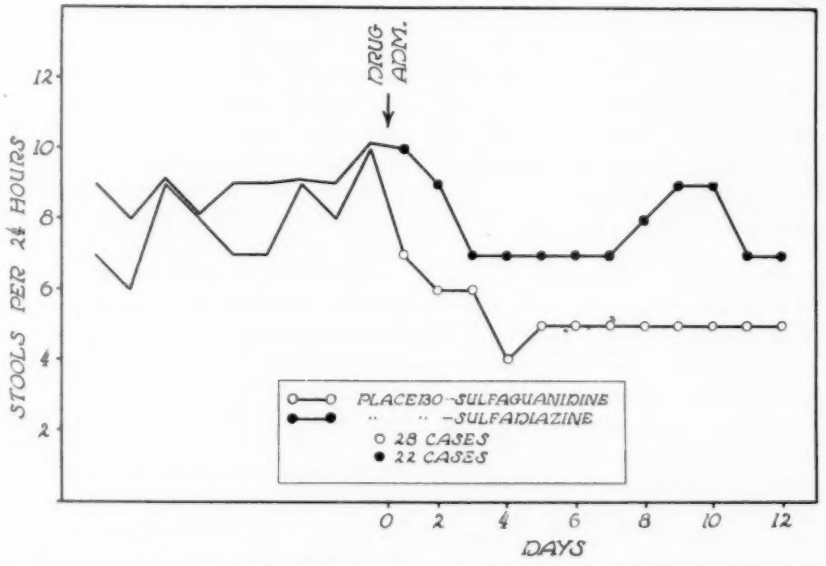

CHART 3.—The average daily stool counts of patients receiving sulfonamide therapy after a preliminary period without medication.

Complications of Sulfonamide Therapy. No untoward reactions to sulfaguanidine were observed. In 10 instances gross urinary complications were encountered in the cases receiving sulfadiazine. Hematuria occurred most frequently, costo-vertebral angle pain, dysuria, oliguria and anuria were complained of in descending order of frequency. Three patients receiving sulfadiazine became totally anuric for from 3 to 5 days; they developed azotemia, severe costo-vertebral angle pain, and vomiting. They appeared to be in critical condition. Two required ureteral lavage,

These results are so at variance with the experience of most other observers that the reasons for their divergent nature require consideration. The first possible explanation lies in the fact that the treatment was begun, on the average, 5 days after the onset of symptoms. This was relatively late in the course of a disease, which, untreated, usually lasts only 2 weeks. It is well recognized that dysentery organisms tend to disappear quite rapidly from the stools of untreated cases, and it is reasonable to assume that unless therapy is begun early little beneficial effect can be expected. The failure to observe favorable effects from sulfonamide therapy cannot, however, be wholly attributed to its relatively late administration, for many of our patients were treated initially on the 1st or 2nd day of the disease. An analysis of the result of therapy in this group gave no indication that it was superior to that which was begun on the 5th day of the disease.

A second possible explanation for our negative results could rest on the fact that we were dealing with such a mild form of the disease that the beneficial effects of drug therapy were difficult to measure in objective terms. It is apparent that we were dealing with a relatively mild form of dysentery since our mortality was *nil* and only 10% of our patients were regarded as seriously ill. This differs widely from the picture described by others, especially of epidemics in wartime. The mortality from the disease in the United States is approximately 5% and in 6 states between 1933 and 1937 it was 15.7%.[2] This possible explanation however does not appear to us to be adequate. It would be misleading to imply that our cases were so mild that amelioration of their clinical condition could pass undetected. For even the cases classed as mild had marked abdominal pain, dysentery, and frequently were febrile, prostrated and occasionally in mild shock. The disease required 10 to 14 days to run its course, and it is inconceivable to us that a significantly beneficial effect from drug therapy could have escaped unnoticed.

It is unfortunate that the conditions under which these observations were made were such that it was not feasible to obtain more than a single stool culture in each case. The percentage of bacteriologically proved cases of bacillary dysentery would undoubtedly have risen with more intensive bacteriologic study. However in our opinion this limitation is not serious for 3 reasons, first, because the result of our study in the clinically diagnosed group was identical with that in the substantial group of bacteriologically proved cases, second because of our conviction, after an extensive experience with the disease, that the former group were, in fact, true cases of bacillary dysentery; and finally, because the patient with acute dysentery but with a negative stool culture presents precisely the same clinical and therapeutic problem as does the patient with a positive culture.

A parenthetic comment concerning the relative virulence of the organisms in the dysentery group deserves mention. It is generally held that *Sh. dysenteriæ* produces a more severe form of the disease than do the other organisms in the dysentery group. This has not been our experience. An attempt was made to predict, on the basis of the severity of the clinical manifestations, what type of organism would be isolated on stool culture. We were totally unable to demonstrate that *Sh. dysenteriæ* produced a more fulminating form of the disease than did other organisms of the genus Shigella.

With respect to the toxic effects of the sulfonamides we observed no ill effects from the administration of sulfaguanidine. However, the renal complications from the use of sulfadiazine were rather frequent and, in several instances, alarming. This is scarcely to be wondered at in a disease of which dehydration may be a feature and in a locality where very high temperature prevails, and under circumstances in which meticulous attention to fluid intake and urinary sediment were not pos-

sible. In all probability we would have had 2 fatalities from ureteral blockage if facilities for ureteral lavage had not been available. In the conditions which prevailed during this study it was our impression that the danger of sulfadiazine in the dosage administered exceeded that of the disease for which it was employed.

We wish to emphasize the fact that these observations relate only to the effects of sulfadiazine and sulfaguanidine on the clinical course of acute bacillary dysentery, and in no sense cast doubt on the advisability of the administration of these drugs to reduce the carrier rate following the acute stage of the disease. It has been amply demonstrated by various observers[1,3,4,6] that the incidence of positive stool cultures during and following the disease can be materially reduced by the administration of sulfonamides. Unfortunately the conditions under which our observations were made did not permit studies on the carrier rate or relapse rate in our cases. But the observations of others have demonstrated conclusively that these can be substantially reduced by doses of the sulfonamides which are smaller than those now recommended for treatment of the acute stages of bacillary dysentery. However our experience has convinced us that the desirability of administering these drugs is dictated by public health considerations rather than by the immediate clinical benefit which may be anticipated.

Conclusions. The efficacy of sulfaguanidine and sulfadiazine in the treatment of acute bacillary dysentery has been studied in approximately 300 Chinese soldiers in India. Neither drug shortened the course of the disease, ameliorated the symptoms nor altered the eventual outcome. The danger of renal complications following the administration of sulfadiazine in our opinion contraindicates its use in the dosage employed under the conditions which prevail here. These observations do not apply to the demonstrated value of these drugs in reducing the carrier rate following acute bacillary dysentery.

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INFECTIOUS POLYNEURITIS (GUILLAIN–BARRÉ SYNDROME)

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THE recent discussions of acute anterior poliomyelitis, stimulated by the introduction of the Kenny method of treatment, and the widespread prevalence of the disease during the season of 1944 have aroused interest in the Guillain-Barré syndrome because the latter enters into the differential diagnosis of poliomyelitis. Whether the Guillain-Barré syndrome may be classed as a distinct entity, as most recent writers believe, or whether it represents a variation of poliomyelitis due to diverse causes cannot be stated at present. One clinical fact emerges from the mass of data concerning both entities: The Guillain-Barré syndrome bears a far more favorable prognosis than does poliomyelitis. That fact in itself is justification for inclusion of the Guillain-Barré syndrome in the diagnostic possibilities of any despondent, acutely ill, paralyzed patient.

The diagnosis of the Guillain-Barré syndrome is based on the clinical picture, the albuminocytologic dissociation of the spinal fluid, and the progress of the illness. In view of the fact that the etiology and true nature of the disease remain obscure, the disease yet constitutes a syndrome in the true sense. Probably few diseases in clinical medicine possess as many appellations as does this entity. The more commonly employed synonyms in the American literature are listed.* No term is entirely applicable. As will be evident in a moment, there is little proof that the disease is *infectious* or *infective*. Neither is it always *febrile*, and in some instances it cannot strictly be said to be *acute*. Upon close analysis the term *neuronitis* differs little in meaning from *neuritis*. Descriptive terms, such as *ascending*, *facial diplegia*, *albuminocytologic dissociation*, while correct in some cases, do not suffice to indicate the protean manifesta-

* Acute febrile polyneuritis; infective polyneuritis; acute polyneuritis with facial diplegia; myeloradiculitis; polyradiculoneuritis; acute infectious neuronitis; radiculoneuritis; acute benign infectious myelitis; meningoradiculomyelitis; encephalomyeloradiculitis; Guillain-Barré syndrome; Guillain-Barré-Strohl syndrome; facial diplegia with polyneuritis; myeloradiculoneuritis; acute ascending paralysis; infective neuronitis; radiculoneuritis with acellular hyperalbuminosis of cerebrospinal fluid; acute infective polyneuritis; polyneuronitis; motoneuronitis; Landry's ascending paralysis; acute infective meningomyeloneuritis; acute toxic polyneuritis; polyneuritis of unknown etiology; acute ascending necrotic myelitis.

tions of the disease. The term *motoneuronitis* connotes little in the clinical sense. Other terms, or combinations of terms, are based upon the assumed pathology of the disease and again disregard the paucity of our knowledge of this entity as well as the visceral pathologic changes recently described by Sabin and Aring.[51] Use of Landry's name in connection with this disease would have sufficed if Landry's original case[36] had been proved. Recently Brown[7] has contended it was nothing more than polyneuritis of beriberi following starvation in an acute infection. The names of Guillain and Barré are closely linked with this syndrome. It is by this latter appellation that the disease is best known both in the American literature and in the foreign reports. Certainly they can be credited with first discerning the albuminocytologic dissociation of the cerebrospinal fluid[26] as well as with a recent comprehensive review of the subject.[25]

Historical Comment. Osler,[44] in 1892, rendered the first lucid description of this entity under the name of *acute febrile polyneuritis*, and pointed out the difficulties in distinguishing between this entity and Landry's ascending paralysis. In 1898 Mills[42] introduced the term *neuronitis* to designate involvement of the entire neuron by the pathologic process. Buzzard,[8] in 1907, reported several cases under the caption of *acute toxic polyneuritis*, and Laurans[37] in the following year commented on the occurrence of facial diplegia in the course of *infectious polyneuritis*. In 1916, Patrick[45] reported 2 cases of facial diplegia in patients with multiple neuritis and thus focused additional attention on the possibility that the 7th or another cranial nerve might be involved in this disease. In the same year Guillain, Barré and Strohl[26] recognized the high protein and low cellular content of the cerebrospinal fluid (albuminocytologic dissociation) and emphasized the equally significant fact that the prognosis was favorable.

Holmes,[31] in 1917, reported the clinical picture as seen in 12 patients together with the pathologic findings in 2 of them. Holmes used the term *acute febrile polyneuritis* to designate the disease. A year later, Bradford, Bashford and Wilson[6] published a comprehensive monograph on the subject and summarized the observations of 30 cases. Most of the cases reported by Bradford manifested involvement of the facial nerve and the cerebrospinal fluid was considered normal in each patient. His series disclosed a mortality of 26.6% and he noted that the patients remained remarkably free from cerebral or mental symptoms even *in terminus*. Bashford discussed the pathologic anatomy of the disease both in man and in the monkey and thought that the pathologic process in both was similar. He likewise thought that he could transmit the disease from man to monkeys as well as from monkey to monkey by subdural inoculations of glycerin emulsions of the involved spinal cord. Wilson went so far as to advance the belief that the causative organism was a virus which he could cultivate from the affected spinal cords of both man and monkey. Arkwright,[3] in 1919, definitely disproved this theory by showing that the globoid bodies which Wilson and his associates had recovered were contaminants.

In 1919, Foster Kennedy[35] reported 4 cases and chose to reintroduce the term *neuronitis*. Summarizing the observations of cases occurring among the troops of World War I, Casamajor[9] suggested the term *acute infective meningomyeloneuritis*. The spinal fluid examinations in his cases were within normal limits.

Recognition of the disease followed rapidly thereafter. Viets,[60] in 1927, reported 2 cases and described the pathologic findings in 1. Both of his cases had facial diplegia and albuminocytologic dissociation. Collens and Rabinowitz,[12] in 1928, reported an instance of polyneuritis with facial diplegia occurring 3 weeks after an episode of mumps. They observed in their case a high protein content of the cerebrospinal fluid without cells and collected 4 similar cases from the literature. In 1934, Urquhart[59] reported an instance

of the disease which followed the onset of measles by 1 week. These and similar observations that the disease is preceded in a substantial percentage of the cases by an upper respiratory infection have served to focus attention on a possible infectious, perhaps viral, origin of the disease. Because of the desirability of the differentiation of the disease from acute anterior poliomyelitis, increasing reports concerning sporadic cases have appeared in both the American and foreign literature. For comprehensive reviews of the subject the reader is referred to the papers of Guillain,[25] Gilpin, Moersch and Kernohan,[23] Hecht,[28] Roseman and Aring,[48] Sabin and Aring,[51] Forster, Brown and Merritt,[16] Fox and O'Connor,[17] and Hatoff.[27]

Etiology. Most writers agree that this syndrome is probably infectious and viral in origin. Proof for this assumption, however, has not been forthcoming. We have already cited the efforts of Bashford and Wilson[6] to isolate an organism from the involved spinal cords of their cases. Arkwright[3] and later Sabin and Aring[51] have disproved their findings; in fact, in an addendum to Arkwright's paper, Bashford and Wilson retracted their original statement. To date no one has succeeded in culturing an organism from the affected spinal cords or viscera of patients with this disease or in transferring the disease to animals. Sabin and Aring[51] have reviewed their unsuccessful efforts to produce the disease in mice, guinea-pigs, rabbits and monkeys. It is of interest that Cobb and Coggeshall[11] believed the necropsy findings of the few patients that had been studied to be compatible with a virus infection of the central nervous system, a view which has been accepted in most part by later investigators. The evidence, therefore, concerning the etiology of this condition remains presumptive.

Beginning with Osler, most writers have emphasized either the infectious type of onset of this disease or the relationship of this condition to an antecedent infection. In a review of the literature, Fox and O'Connor[17] found that 49 of 122 cases had a history of a preceding illness, such as coryza, aches and pains, and gastrointestinal disturbances. Each of their 4 cases had an infection of the upper respiratory tract prior to the onset of paralysis. Each of the 3 patients that we are reporting herein likewise had an upper respiratory type of clinical picture at or prior to the onset of this condition. As a rule, the infection precedes the onset of the disease by a week or more but may be present when neurologic symptoms develop. Thus, a latent period between the preceding infection and the development of neurologic manifestations may or may not be demonstrable.

The type of infection initiating this trend of events varies considerably. The syndrome has been known to be precipitated by or supervene in systemic infections[27] such as encephalitis, measles, diphtheria, mumps, mumps complicated by orchitis, mastitis, scarlet fever, influenza, pneumonia,[48] chicken-pox, botulism and syphilis, and recently infectious hepatitis. Hiller and Fox[30] have recently noted the association of this entity with infectious mononucleosis and suggest that a heterophil antibody determination be obtained on every patient with the Guillain-Barré syndrome. In addition, coëxistence of this disease has been noted with various foci of infection: Vincent's angina, tonsillitis, dental caries and abscessed teeth, perianal abscess, osteomyelitis, epidural abscess and furunculosis. Primary development of the disease without preceding infection can be demonstrated in a small percentage of cases.

As previously stated, the inciting organism has not been established nor are the mechanisms clear by which this syndrome results from such a diversified group of unrelated infections. The weight of opinion leans toward the viral origin of this disease and it is thought that a neurotropic virus[23,51] is in some way activated by the antecedent infection. Whether such a virus is already present in the central nervous system or whether it is

introduced by the associated infection remains obscure. Other organisms have received consideration as active causes for this entity, particularly staphylococci,[5] streptococci[38,49] and *Hemophilus influenzæ*.[5] In such instances the toxic etiology, as suggested by Heernu[29] and Sabin and Aring[51] offers the most satisfactory explanation for the neurologic phenomena. Such a circulating toxin may be elaborated by the microörganisms producing the respiratory infection and possess an affinity for the peripheral as well as the central nervous system and viscera. Sahs and Paul,[52] on the other hand, state that the available evidence points primarily to an intoxication of the peripheral nervous system rather than to an actual infection.

In a syndrome in which a definite incriminating factor cannot be demonstrated and in which the pathologic changes may vary widely, it is, of course, logical that other causes for this clinical picture may be found. In other words, this syndrome may be secondary to some entity of greater importance. Among these are serum sickness,[43] sulfonamide intoxication,[27,39] tuberculosis,[20] leprosy,[18,46] cervicodorsal arthritis, diphtheria, diabetes,[46] and artificial fever.[21] The resemblance to myasthenia gravis has likewise been emphasized. Thus, patients with this entity should be studied carefully to exclude demonstrable organic disease both in the central nervous system and elsewhere throughout the body. Careful inquiry into the medical history as to dietary deficiencies and assimilation of heavy metals such as lead, mercury or other noxious agents is likewise indicated from the etiologic point of view. Suffice it to say that the more careful the diagnostic investigation, the fewer cases of primary origin will be revealed.

Little information concerning the etiology of this condition has been derived from the clinical incidence. As a matter of fact, it is difficult to obtain any satisfactory values for the incidence of the disease. The large number of synonyms employed renders an analysis of the literature or hospital records almost fruitless. Gayle and Groom[22] estimated in 1943 that probably 50 cases of this entity had been studied, but Fox and O'Connor[17] 1 year earlier collected 122 cases from the literature and since their report several papers on this syndrome[1,2,4,10,13–15,19,22,27,30,33,34,43,47,50,52–55,61] have appeared in the American literature, not to mention foreign reports. That the disease is sporadic and seldom epidemic seems true although recent observations suggest that mild epidemics may occur. Reports vary concerning the seasonal incidence but the bulk of the evidence indicates that the greatest incidence occurs during the variable weather of the cold seasons, a time during which acute anterior poliomyelitis is not likely to attain its maximum distribution. It shows equal predilection for both sexes and for all age groups. So many cases have been described in the age groups less than 20 years that Susman and Maddox[57] termed this entity an apyrexial disease of childhood and adult life. It is of interest to note that Brown[7] believed that this disease as a disorder of the nervous system is exceeded in incidence only by alcoholic polyneuritis.

Some have considered this disease as abortive poliomyelitis. Others distinguish between the 2 conditions on the basis of the clinical picture. The points in differentiation have been considered in detail in the section on Diagnosis.

Morbid Anatomy. The pathologic changes of this entity have been studied by Holmes,[31] Bradford, Bashford and Wilson,[6] Casamajor,[9] Viets,[60] Greenfield and Carmichael,[24] Gilpin, Moersch and Kernohan,[23] Sabin and Aring,[51] Honeyman,[32] and Roseman and Aring.[48] Although the earlier writers devoted their attention chiefly to the pathology of the nervous system both centrally and peripherally, the later writers, particularly Sabin and Aring and Roseman and Aring, have emphasized the visceral changes as well, which indicate the protean manifestations of this disease. The pathologic alterations

of the nervous system will be summarized first. In general, there is macroscopically a moderate degree of edema of the brain, spinal cord, and peripheral nerves with slight vascular congestion of the overlying leptomeninges of the brain and spinal cord. Fairly uniform changes may be found in the peripheral nerves. These consist microscopically of marked edema of the bundles, congestion, focal infiltration of inflammatory cells, swelling and beading of the myelin sheaths, and fragmentation, beading and dissolution of the axis cylinders. Involvement of the gray columns of the cord may be found in nearly all cases with the most marked changes at the cervical and thoracic levels. The anterior horn cells likewise show varying changes including widening of the perineuronal spaces, chromatolysis, and vacuolization of the cytoplasm. Changes of a similar nature may be found in the other fiber tracts of the cord and brain stem. In some instances the morbid process appears diffuse, in others spotty, and in a few cases scant or no changes can be demonstrated. In the cerebrum and cerebellum, the abnormalities have been described as slight "outfall" of nerve cells, shrinkage of the ganglion cells with poor staining qualities of both the cytoplasm and nuclei, congestion, swelling of the oligodendroglia of the white matter, and slight inflammatory reaction of the meninges.

It seems clear that the pathologic changes described above are more severe in the peripheral and cranial nerves. Indeed, the changes in the central nervous system may be interpreted as mild in character and perhaps secondary to those of the peripheral nervous system. That these changes are readily reversible likewise appears evident. One point is worthy of emphasis as support for this statement: Neuronophagia is relatively rare in the brain and spinal cord as compared to the marked degree of phagocytic reaction in the peripheral nervous system. The Nissl substance is likewise well preserved centrally as contrasted to dissolution peripherally.

Sabin and Aring[51] have summarized the visceral manifestations of this syndrome. Briefly these consist of acute passive congestion and toxic changes of the liver, kidneys, heart and spleen. Some fatty infiltration of the liver may be noticeable about the central vein areas. The adrenal gland in 1 of their cases revealed widespread softening on gross examination, whereas the microscopic studies disclosed significant abnormalities in the adrenals of all cases. These consist chiefly of patchy areas of degeneration, infiltration with plasma cells and lymphocytes and vacuolization. The lungs revealed bronchitis in all their cases with some patchy lobular pneumonia, varying areas of atelectasis and compensatory emphysema. The visceral changes are of such a character as to resemble closely the changes in typhoid fever and diphtheria in which a circulating toxin may be held responsible. In fact, Sabin and Aring have compared these changes to those produced by a pantropic virus. These changes, in view of the etiologic relationships discussed previously, point strongly to the microorganisms found under certain conditions in the upper respiratory tract as causative factors. Proof that these pathologic findings may be produced by the toxins elaborated by these organisms has not been demonstrated but the theory does open a trend for additional investigation.

Clinical Picture. In a syndrome characterized by widely divergent precipitating factors and resulting in atypical, varied pathologic changes, it is remarkable that the clinical picture is as clearly defined as it is. In their original paper purporting to present a new syndrome, Guillain, Barré and Strohl[26] outlined what they considered to be the typical course of the disease. Guillain[25] has recently amplified this description of the clinical picture. Not all writers are in entire agreement with Guillain, particularly with regard to his belief that all cases must present albuminocytologic dissociation of

the cerebrospinal fluid and that all cases recover. With minor exceptions, however, the clinical picture seems to be fairly characteristic. We shall, therefore, present a composite picture of the disease as it is described in the literature.[1,2,4,10 13–15,17,19,27,33,34,43,47,48,50,52–55,61]

As discussed previously, the onset is usually heralded by some upper respiratory infection in the form of a cold, grippe or influenzal syndrome. Mild generalized aches and pains, usually most pronounced in the calves of the legs and in the back, are frequent prodromata, as is headache. The latent period intervening between the symptoms of infection and the appearance of neurologic manifestations may vary from a few days to several months, averaging 1 to 3 weeks. The earliest neurologic symptoms are usually referable to the sensory system. The pain in the back and legs may be confused with rheumatism or lumbago, but occasionally the pain may be of such severity as to require sedation. Muscle and nerve tenderness are invariably present. Paresthesias, particularly numbness of the hands or feet, are frequent. Characteristically, the sensory disturbances are limited to the distal portion of the extremities and diminish in severity as one advances proximally. Objective sensory disturbances may be elicited shortly after the onset as denoted by impairment of vibratory sense and diminished perception of pain and light touch.

In general the motor disturbances appear any time within a few hours to as long as 1 week after the onset of the sensory phenomena and may develop insidiously or rapidly. The motor disability is usually bilateral, symmetrical and progressive. In contrast to the sensory disturbances, the motor signs are more striking in the proximal than in the distal musculature. Once developed, the motor disturbances completely overshadow the sensory changes. A flaccid paralysis ensues which may progress to quadriplegia. Both the rapidity and the degree of paresis vary considerably from slight muscular weakness and awkwardness to complete helplessness in a patient in whom all voluntary movements have been lost except for a slight wriggling of the fingers and toes. These changes may develop within a few days or require weeks to attain the full blown picture with occasional periods of remission. Additional generalizations are permissible: Wasting or atrophy of muscle segments seldom occurs except that induced by disease; fibrillary movements are seen infrequently; involvement of the trunk, intercostal muscles, or diaphragm renders the outlook exceedingly grave.

Other neurologic manifestations are not characteristic. The tendon reflexes are either diminished or absent. The abdominal reflexes may be diminished or unaffected. No pathologic reflexes can be elicited. The sensory disturbances, namely impairment in the sense of vibration and diminished perception of pain and light touch, have been mentioned. Involvement of the rectal or vesical sphincters occurs only rarely, except in children and in the moribund. Cranial nerve involvement occurs in a high percentage of cases. Bilateral or unilateral facial paralysis is frequent and is often overlooked in the bilateral types. This is nuclear or infranuclear in origin so that the brow and eyelids are involved as well as the lower portion of the face. Other cranial nerve involvement may be manifested by blurring of vision, nystagmus, palatal paralysis, dysphagia, dysphonia, difficulties in mastication, anosmia, deafness, tinnitus, vertigo, lingual deviation, and impaired taste. Papilledema and optic neuritis may be found infrequently. Pediatricians writing on this subject have stressed the euphoric state of children[57] but in adults and the more severely ill, depression or delirium are more common.

Though the disease does affect the viscera, as determined by postmortem examinations, constitutional or systemic manifestations other than those discussed above are infrequent and usually mild in character. The temperature seldom ex-

ceeds 102° F. and that elevation occurs usually in the 1st week of the illness. A mild tachycardia is noted in the majority of patients even in the absence of fever, although it is increased proportionately to the temperature elevation when such occurs as well as in the dangerously ill patients. Other symptoms are rarely present except as complications resulting from the original or secondary infections, such as pneumonia. McIntyre[40] has recorded electrocardiographic evidences of a toxic myocarditis in a patient with this syndrome.

Course and Prognosis. The course of the illness is quite variable. In general the duration may be stated to vary from 2 weeks to 3 years or more. Convalescence is usually slow and, as a rule, recovery of function follows the same order in which it was lost. Occasionally recovery is rapid and progressive as in Case 1 of our patients. Some patients never regain a complete sense of well-being and vigor. Others manifest only slight residual defects such as weakness of one side of the face. Still others (Case 2 of our group) have paralytic phenomena as long as they have been observed. By the original postulates of Guillain, Barré and Strohl,[26] and later Guillain,[25] recovery should occur in every patient for the disease in question to be compatible with their syndrome. Whether they were dealing with a benign form of the disease in their series of patients or whether the diagnoses in the patients of other investigators, including Case 2 of our group, were incorrect, cannot be answered in the present state of our knowledge. Certainly the preponderance of opinion indicates that this syndrome is not at all as benign as Guillain and his group believed. Those observers with large groups of patients to evaluate report varying statistics concerning the mortality rate. Thus Gilpin, Moersch and Kernohan[23] recorded 14%; Roseman and Aring,[48] 18.8%; and Forster, Brown and Merritt,[16] 42%. In a survey of the literature as a whole, Fox and O'Connor[17] concluded that the mortality rate was approximately 20%. Death occurs within the first 2 weeks of illness and may be attributed in most part to respiratory paralysis. Recurrences of the disease have not been observed.

In general the prognosis is uniformly good in children. In adults the involvement of the intercostal muscles, abdominal musculature and diaphragm seriously affects the prognosis. It has been the experience of most writers that recourse to the respirator bears grave prognostic significance. Immediate recognition and correction of any accompanying disease or foci of infection, of course, improves the prognosis. Other than these factors, little of prognostic value can be learned from the individual patient.

Diagnosis and Differential Diagnosis. In the diagnosis of this condition much weight is given the laboratory findings of the cerebrospinal fluid. In their original paper, Guillain, Barré and Strohl[26] described the elevated protein content of the cerebrospinal fluid with no increase in cellular content (albuminocytologic dissociation) and these findings have been adhered to by the French writers and others as essential features of the diagnosis. In fact, Guillain[25] flatly stated that the protein determination must exceed 300 mg. to fit this syndrome. Whereas an elevation of the protein content of the cerebrospinal fluid does occur in most instances, this is by no means invariably so nor does it indicate definitely the existence of this syndrome. From recorded cases in the literature it would appear that the protein values may range from 70 to 800 mg. or more (Case 3). In general, the elevation of the protein occurs during the acute phase of the illness, usually within the first 2 weeks. Stone and Aldrich[56] have reported 2 cases in which the determinations were rather low at the onset of the illness but attained higher values as the disease pursued its course (7th and 14th days, respectively). We observed similar findings in Case 2. Once established, the elevated protein content may persist for several years.

Roseman and Aring[48] report 1 patient whose spinal fluid protein determination had been elevated throughout 5 years of observation.

Other spinal fluid findings are usually within normal limits. The fluid is characteristically clear, xanthochromia being observed but rarely. The Pandy test for globulin is usually positive. The cell count generally reveals either an absence of cells or a slight increase up to 25 cells, all of which are lymphocytes. The spinal fluid pressure is usually normal or slightly elevated, varying as a rule from 150 to 220 mm. of water. The colloidal gold curve is generally low and non-specific.

As stated, the interpretation of the elevated protein content of the cerebrospinal fluid without a cellular response is a moot question. There is scarcely a chronic disease of the central nervous system which does not manifest an elevated protein (albumin) value at some time throughout its course. Thus, an albuminocytologic dissociation may be observed occasionally in poliomyelitis although the protein values do not usually attain the high levels observed in the Guillain-Barré syndrome.

Postdiphtheritic polyneuritis may be differentiated by the clinical history and by smears and cultures of the nose and throat. Syphilis may be excluded by the colloidal gold curve and by blood and spinal fluid Wassermann reactions as well as by other clinical stigmata of this disease. Muscular atrophies and dystrophies seldom provoke an acellular hyperalbuminosis and then only to a mild degree (100 mg. of protein or less). Tumors of the central nervous system offer more difficulty; alterations in pressure relationships and changes in the motor and sensory responses may be evident and permit localization of the growth. These examples will suffice to indicate that the cerebrospinal fluid findings must be interpreted with the history and clinical picture at hand before a correct diagnosis can be made. As emphasized by Cobb and Coggeshall[11] and later by Merritt and Fremont-Smith,[41] the cerebrospinal fluid may be entirely normal. Figures vary but Merritt and Fremont-Smith found normal protein values in 8 of 30 patients with this syndrome.

Other laboratory findings are non-contributory. There is usually a mild leukocytosis, the white blood count varying from 10,000 to 15,000 cells with a mild increase in polymorphonuclear cells. The urine generally reveals normal findings, though occasionally a transient albuminuria may be detected.

As discussed under the etiology of this condition, the diagnosis is permissible only when other contributing factors, such as dietary insufficiency, alcoholism, poisoning by lead, mercury or other heavy metals, and the like, can be excluded. In other words, the syndrome must be a primary condition or the polyneuritis must be of unknown etiology in order to establish this diagnosis. Differentiation from acute anterior poliomyelitis becomes of paramount importance. That acute anterior poliomyelitis may at times be characterized by ascending paralysis was suggested by Wickman[62] who found such disturbances in 32 patients of 868 epidemic cases of poliomyelitis. Some of these, however, may have been instances of the Guillain-Barré syndrome for such differentiation was not made at the time of Wickman's monograph. The question arises as to whether these two entities are essentially variants of one another. The evidence is weighty on both sides of the discussion. Until more is known about the etiology and pathogenesis of acute anterior poliomyelitis as a disease entity, recognition of the Guillain-Barré syndrome as a distinct entity is warranted, if for nothing more than the better prognosis that it affords in comparison to poliomyelitis. Certainly the hope and outlook that the physician may offer the paralyzed patient with the Guillain-Barré syndrome are distinctly better than the prolonged convalescence and atrophy of the muscle groups seen in poliomyelitis. The differentiation of these two entities

has been discussed by most writers, particularly De Sanctis and Green,[13] Sahs and Paul,[52] and Gayle and Groom.[22] It is fitting, therefore, that we summarize the differences in clinical data obtained from both groups of patients.

The essential differences are these: Acute anterior poliomyelitis has a distinct seasonal incidence, usually from August through October; the Guillain-Barré syndrome is most prevalent throughout the colder months of the year, though cases may be seen at any time. Poliomyelitis is usually epidemic; the Guillain-Barré syndrome is usually sporadic and rarely epidemic. Poliomyelitis attains its highest incidence in children during the first 2 decades of life; the Guillain-Barré syndrome occurs in all age groups with the mean average during the 3rd decade. The Guillain-Barré syndrome is preceded by an infection in more than 50% of the cases and the systemic manifestations usually subside before the neurologic phenomena appear, in which event evidences of meningeal irritation are usually inconspicuous. In poliomyelitis, on the other hand, the systemic manifestations are usually followed rapidly by signs of meningeal irritation and paralysis. Although patients with the Guillain-Barré syndrome complain of paresthesias and tenderness along the nerve trunks in variable degree, pain and muscle spasm are not nearly as marked as in poliomyelitis. Whereas the Guillain-Barré syndrome has been repeatedly described as a bilateral, symmetrical and progressive paralysis of the lower extremities with more severe involvement of the proximal group of muscles than of the distal ones, poliomyelitis may be characterized as an asymmetrical, segmental, "spotty," rarely ascending paralysis involving predominantly the hamstrings, gastrocnemius, biceps and back muscles. In 35 to 50% of all cases of the Guillain-Barré syndrome the cranial nerves, particularly the facial, are involved, usually bilaterally but occasionally unilaterally. Involvement of the cranial nerves is rare in poliomyelitis. The spinal fluid findings in most instances of poliomyelitis characteristically reveal a moderate increase in the total protein content and a pleocytosis which is most marked in the preparalytic stages and falls rapidly once paralysis ensues. Final differentiation of the two entities will be established by the course of the illness. Patients with the Guillain-Barré syndrome may experience a slow, chronic progression of the paralysis over a period of several weeks then gradually recover, provided respiratory failure does not supervene. In poliomyelitis, to the contrary, additional involvement rarely occurs after the 2nd week of illness. Toomey[58] has stated that any patient with a massive paralysis lasting several weeks followed by recovery does not have poliomyelitis. Moreover, there are no distinct objective sensory changes in poliomyelitis such as may appear in the Guillain-Barré syndrome.

Treatment. Treatment is supportive and symptomatic. In view of the fact that this entity is self-limited and accompanied by a high degree of recovery, it is difficult to evaluate any form of treatment. In the early phases of the illness, attention should be directed toward the alleviation of pain and the maintenance of adequate fluid intake and nutrition. Nursing care is especially important, particularly for those in whom involvement of the rectal or vesical sphincters has occurred as well as for those with respiratory difficulties. Occasionally use of the Drinker respirator as well as repeated aspiration of mucus from the respiratory passages is indicated. Reassurance and the maintenance of morale becomes an important duty of the attending physician. Protective splints should be applied to prevent any undue contracture or elongation of paretic muscles. As the acute stages pass, physiotherapy in the form of active and passive exercises, hydrotherapy and massage should be instituted. The Kenny method has been employed by several investigators[2,19,32] without any conclusive results.

Specific drugs offer little in the therapy of this condition. Numerous agents have been reported in the literature. De Mello, quoted by Hatoff,[27] and Roseman and Aring[48] have used vitamin B_1 intravenously. The dosages employed by the latter consisted of 50 to 100 mg. of thiamin chloride daily for a period as long as 3 weeks. The only benefits observed were relief of the sensory changes, such as pain and paresthesias, in 6 of 9 patients so treated without any effect upon the motor changes. Guillain[25] recommended several agents: intravenous infusion of sodium salicylate in serum with 10% dextrose, intravenous or intramuscular quinine, methenamine, or colloidal silver. Other empirical measures[27] include rubs with colloidal silver, ionized iodine or calcium administered by the transcerebromedullary route, warm baths and irradiation. Plügge is reported by Hatoff[27] to have obtained good results with physiotherapy and electrical stimulation. According to Wolf,[63] prostigmin shortens the duration of lower motor neuron paralysis and should be tried in this syndrome. Correction of any contributory or accompanying disease is, of course, indicated. Certainly the physician should weigh carefully the potential hazards attendant upon the administration of any drug on an empirical basis for the therapy of this condition.

Case Reports. The following case reports, presented in detail, will illustrate the clinical picture and the difficulties in the diagnosis and treatment of this syndrome.

Case 1. C. M., a 54 year old white male, was admitted to Charity Hospital on Oct. 18, 1943, with chief complaints of marked weakness of hands and legs and numbness of fingers and feet. He stated that he had had an acute onset of a cold and pain in his back 3 weeks previously. The cold had subsided before admission but the pain in the midline region of his back persisted. On admission, pain of a dull aching type radiated over the chest and abdomen. The onset of numbness of the hands and feet had been gradual. He had noted no fever and no tenderness.

On admission the physical examination disclosed general muscular weakness. The patient was unable to sit, stand or walk. Knee and ankle reflexes were absent but no pathologic reflexes were elicited. No sensory changes were found. The urinalysis, blood Wassermann reaction, and electrocardiogram were normal. The spinal fluid survey disclosed an initial pressure of 200 mm. of water with clear fluid, normal dynamics, less than 10 cells, 111 mg. of protein, 65 mg. of glucose, and 727 mg. of chlorides. The Kline and Kolmer tests were negative and the colloidal gold curve was 1122331000.

Therapy consisted of bed rest, nursing attention, a diet high in calories and vitamins, warm whirlpool hydrotherapy to all 4 extremities daily, and thiamin chloride in therapeutic doses by mouth. No fever was noted at any time. The patient's course in the hospital was marked by gradual and steady improvement in the motor functions of the extremities. He was discharged on Nov. 11, 1943, able to walk, stand and sit up, although ankle jerks were still missing. On December 6, the patient was seen in the clinic for a progress visit and appeared sufficiently well to resume his work.

Case 2. A. P., a 42 year old white male, was admitted to Charity Hospital on Oct. 23, 1942, complaining of inability to void, pains in the back and chest, and numbness of both legs. He stated that he was healthy until the gradual onset of pains in the legs, arms and front of chest at night about 3 weeks previously. The following day he developed a mild cough, which was productive of a little phlegm. He remained in bed at home under the supervision of his family physician but without much change in clinical picture. Two days prior to admission to Charity Hospital, he suddenly became unable to void. His physician catheterized him the following day and he had been unable to void since without catheterization. On the day prior to admission he noted a numb sensation in his left leg. This numbness began by involving the left thigh, gradually extended to include all the left leg, so that at the end of the day he could not walk. Numbness of the perineum was noted. On the day of admission numbness also involved the right leg and extended up the trunk to a level about 1 inch above the umbilicus. The patient stated that he could move the affected parts to some

extent but could not feel them move. Bowel movements were unchanged.

Physical examination revealed a temperature of 100.2° F. Rhonchi were noted throughout the chest. Neurologic examination revealed bilateral sustained ankle clonus, impaired sensation in both legs for sharp and dull objects up to the umbilicus. Temperature sensation was unimpaired. All deep reflexes were active and equal. Abdominal reflexes were absent and Babinski reflexes were positive bilaterally.

Upon admission the urinalysis was normal and the blood revealed 65% hemoglobin, 3,900,000 red cells, 22,850 white cells (95% neutrophils, 2% lymphocytes, 1% monocytes, and 2% myelocytes). Kline and Kolmer reactions in the blood were negative on 2 occasions. Roentgenogram of the chest revealed several scattered areas of bronchopneumonia throughout the right lower hemithorax. Pneumococcus Type VI was isolated from the sputum. Treatment with 40,000 units of Type VI antipneumococcic serum and sulfadiazine was initiated. Spinal survey on admission revealed xanthochromic fluid, normal dynamics, 16 cells, mostly polymorphonuclear, per c.mm., and 4+ Pandy test. Sugar was 66 mg., chlorides were 713 mg. and total protein was 516 mg.

On October 25, a second spinal survey revealed similar findings but with absence of cells and protein of 950 mg. Tenderness was noted over the sixth dorsal vertebra. All reflexes were absent but no pathologic reflexes were elicited on October 26. Some improvement of sensibility for sharp and dull discrimination was noted.

Neurosurgical consultation was obtained on October 27 to rule out a transverse myelitis. The lesion did not progress and the level of numbness stayed at the fourth to the sixth dorsal vertebræ. Subsequent spinal tap on November 10 revealed clear fluid, pressure 200 mm. of water, normal dynamics, 2+ Pandy test, and 14 lymphocytes. Blood culture on October 24 and 26 revealed 3 to 10 colonies of *Staphylococcus aureus pyogenes*, considered a contaminant.

During his hospital stay the patient continued to run an intermittent low-grade fever up to 101.5° F. He was discharged on Nov. 28, 1943, and follow-up in December 1943 revealed no change in the neurologic picture.

Case 3. O. T., a 31 year old, colored male, was admitted to Charity Hospital on March 20, 1943, complaining of weakness and numbness in his legs and difficulty in voiding for 4 days prior to admission. Patient was well and vigorous until 10 days previously when he had had general malaise, generalized aching, particularly in his joints, and possibly some fever. He stopped working and went to bed, believing that he had influenza. He was apparently recovering from this episode when, 4 days prior to admission, he noted that he was having difficulty walking. He went to bed and soon noticed that he had difficulty voiding. During the intervening 4 days prior to admission the weakness and numbness of the lower extremities progressed, and finally complete urinary retention developed which necessitated hospitalization of the patient.

Upon admission to the hospital the patient stated that his vision had been growing dim, particularly in his right eye, and that his eyeballs had been somewhat painful. Physical examination revealed a well-developed, well-nourished, colored adult male who did not appear to be acutely ill and who was in no great amount of pain. Temperature was 98.6° F., pulse 80, blood pressure 148/80. Neurologic examination revealed complete paralysis of the left leg and paralysis of the right leg except that he could dorsiflex the foot and toes on the right. No atrophy or muscular fibrillations were noted. Below the second and third lumbar vertebræ there was diminution in all modalities of sensation and absence of position and vibratory sense. Reflexes were hyperactive in the lower extremities, more so on the left, but no Babinski or ankle clonus was obtained. Abdominal reflexes were absent. Spinal fluid survey revealed an initial pressure of 190 mm. of water, clear fluid, normal dynamics, 24 cells, all lymphocytes.

The following day the patient complained of increased pain in his right eye and dimness of vision of that eye. Ophthalmoscopic examination of the right eye revealed a moderately advanced papilledema involving the superior two-thirds of the disk more prominently than elsewhere. Two small capillary hemorrhages were seen on the temporal and superior temporal margins of the disk. There was constriction of the retinal arterioles with marked A–V disproportion. Examination of the left eye was

the same except for absence of hemorrhages. No muscular palsies were noted. Loss of vision continued until, 4 days later, the patient could perceive only light. On April 5, a second spinal survey revealed 130 mm. of water pressure, clear fluid, normal dynamics, 6 lymphocytes, 741 chlorides and total protein of 1140 mg. On April 6, the vision had improved sufficiently so that the patient could see fairly well. Ophthalmoscopic examination revealed regression of the previously described papilledema and resorption of the hemorrhages but A–V disproportion was still noticed.

Laboratory data were as follows: On March 28, 1943, red blood cells were 5,850,000, white blood cells 13,600 (86% neutrophils, 4% monocytes, 10% lymphocytes). On April 5, there were 5,190,000 red cells, 80% hemoglobin, 11,500 white blood cells (62% neutrophils, 1% monocytes, 37% lymphocytes). Urinalysis (retention catheter) revealed numerous white blood cells and red blood cells. Gram stain of urinary sediment showed short chain gram-positive streptococci and gram-negative rods. The Wassermann reaction was negative on 4 occasions. Blood carbon dioxide combining power was 52, urea nitrogen 10.5.

Spinal fluid on March 21 showed 777.9 mg. chlorides, total proteins 407 mg., initial pressure of 190 mm., clear fluid, normal dynamics, 24 cells, all lymphocytes. On April 5, 1943, spinal fluid survey showed 130 mm. of water initial pressure, clear fluid, normal dynamics, 6 lymphocytes, 741 mg. chlorides, 1140 mg. total protein, 46 mg. sugar. On April 12, 1943, spinal survey showed 160 mm. of water initial pressure, normal dynamics, clear fluid, 4+ Pandy test, 950 mg. total protein. On May 4, protein was 114 mg., glucose 60 mg., chlorides 743 mg., Pandy test 2+, 16 cells. On July 23, protein was 163.2 mg., glucose 53 mg., chlorides 717 mg., colloidal gold curve 0000001100.

Roentgen views of the spine on admission revealed no evidence of bone or joint disease.

The course in the hospital was characterized by an irregular low-grade fever, occasionally spiking to 102° F., for 2 months. At no time was the patient seriously ill. About the 4th week after admission decubitus ulcers on the buttocks developed and presented serious nursing problems. An indwelling catheter was left in place for almost 6 months. Therapy consisted of urinary antiseptics, urologic attention to bladder and indwelling catheter, physiotherapy consisting of massage from hips to toes, infrared irradiation, active assistive motion of joints, and sulfathiazole.

Indwelling catheter was removed on Aug. 14, 1943, at which time the patient was able to urinate spontaneously. He was discharged Aug. 18, 1943. No information concerning his recent progress has been obtained since that date.

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NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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We regret that we have to omit the article regularly scheduled for this issue, as the Progress editor was unable to have a manuscript prepared for publication.

PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF NOVEMBER 20, 1945

The Effect of Injection Rate Upon the Anesthetic Dose, Lethal Dose, and Anesthetic Duration of Pentothal in Mice, and Strength-Duration Curves of Depression. MILES H. ROBINSON, M.D. (Dept. of Pharmacology, Vanderbilt Univ.). Using a method of constant rate intravenous injection in mice whereby injection rates over a range of from about 6 to 600 mg./kg./min. was covered, it was found with pentothal that decreasing the injection rate raised both the AD50 and the LD50. Depending on what injection rates are used for these doses, the LD50/AD50 or therapeutic index of pentothal may lie between 3 and 10; and the modified index of Foster, $\left[\frac{\text{LD1}}{\text{AD99}} - 1\right] . 100$, which takes into account the slopes of the dosage-effect curves, decreases to zero with sufficiently slow injection rates. Tentative evidence was secured that a given duration of anesthesia requires a fixed fraction of the margin between AD50 and LD50, regardless of the injection time. The factors of injection rate and injection duration were found to be related in a fairly regular manner for a given criterion of central nervous system depression, approximately according to the expression $y = Kx^{-\alpha}$, in which α varied from about 0.7 to 0.8. From such anesthetic and lethal curves of pentothal, and probably of most other hypnotics, LD50/AD50 can be estimated for any rate or time of injection common to both doses. These strength-duration curves of depression for the animal unit are similar to the strength-duration curves of excitation for the cellular unit, and reasons are given for the appropriateness of the analogy. An incidental finding was that mice raised on whole grains as compared to those raised on an elaborate ground-up pellet diet were found to have a progressively higher lethal dose of pentothal as the injection rate is decreased, amounting to as much as a 50% increase in the lethal dose.

The Analgesic Action of l-Amino-l-phthalidylpropane Hydrochloride. EDWIN J. FELLOWS, PH.D. (Dept. of Pharmacology, Temple Univ.). A new derivative, l-amino-l-phthalidylpropane hydrochloride ("phthalidyl") was appraised in animals from the standpoint of its possible effectiveness as an analgesic agent. These studies disclosed the following:

1. In rats (D'Amour-Smith method) "phthalidyl" elevated the threshold pain stimulus but aminopyrine did not. In cats (Eddy method) the latter induced only a slight elevation of the threshold pain stimulus, whereas "phthalidyl" exhibited marked activity. The acute toxicity of aminopyrine in rats was approximately 3 times greater than that of "phthalidyl."

2. In cats the effective dose range of "phthalidyl" was far in excess of that of demerol, codeine or morphine, although comparable elevation of pain thresholds was observed. "Phthalidyl" appeared to be almost entirely devoid of an excitatory component, whereas demerol, codeine and morphine produced effects which suggested a mixture of excitatory and depressant actions.

3. In experimental animals, the circulatory, gastro-intestinal, cardiac and respiratory actions of "phthalidyl" were found to be negligible. This suggests that its use as an analgesic agent would not be complicated by excessive side effects.

4. "Phthalidyl" evidenced activity when administered orally as well as parenterally.

CONCLUSION. Because of its marked threshold pain stimulus elevating action, low acute toxicity and relative lack of

side effects in animals, 1-amino-1-phthalidylpropane hydrochloride should receive clinical trial as an analgesic agent.

Artificial Respiration: A Comparison of the Schafer, Eve and Meltzer-Auer Methods in Two Apneic, Asphyctic Patients. JULIUS H. COMROE, JR., M.D., and ROBERT D. DRIPPS, M.D. (Dept. of Pharmacology and Harrison Dept. of Surgical Research, Univ. of Penna. School of Medicine and Dept. of Anesthesiology, Hosp. of the Univ. of Penna.). The Schafer prone pressure and the Eve gravity or tilting methods for artificial respiration have never before been compared quantitatively in typical cases of respiratory failure with asphyxia. We were able to compare various resuscitation techniques in 2 patients who had complete respiratory arrest for $2\frac{1}{2}$ and 7 hours respectively. An endotracheal tube was passed through the larynx to ensure an open airway and respiration was measured by applying tightly a full face mask equipped with valves and conducting the expired air through a Bohr meter. The tidal air produced by the Schafer method varied from 71.5 to 117 cc., whereas that produced by the Eve gravity or tilting method varied from 286 to 500 cc. It is apparent that the Schafer method failed almost completely to ventilate these 2 unconscious, apneic and asphyctic patients. Reliance should not be placed on the Schafer method except as a very temporary emergency measure suitable only until more efficient methods can be instituted.

In these 2 patients, an attempt was made to sustain life by the Meltzer-Auer tracheal insufflation method. Oxygen was delivered through a catheter to the bifurcation of the trachea in each patient at a rate of 6 to 11 liters per minute. This resulted in initial arterial oxygen saturations of 95.8 and 90%. However, marked accumulation of CO_2 occurred with consequent acidosis. The CO_2 tensions in the arterial blood rose to 314 and 152 mm. Hg and the arterial pH fell to 6.67 and 6.86, the latter being one of the lowest ever recorded in a living man. Artificial respiration therefore must not only oxygenate the blood but also eliminate excess CO_2; the latter apparently requires rhythmic chest movements.

Measurement of the Heat Exchange of the Foot. LOIS J. HOSBACH, E. S. MENDELSON and H. C. BAZETT, M.D. (Dept. of Physiology, Univ. of Penna.). A calorimeter is described into which the foot can be sealed and the heat output measured. The calorimeter is a double-walled copper vessel which is part of a closed system through which air is circulated. Non-evaporative heat loss can be calculated from the increase in temperature of the air passing through the calorimeter and the temperature difference across the walls. Evaporative heat loss is measured by absorbing the moisture present in the exit air. In use the calorimeter was suspended inside of a refrigerator box so that the environmental temperature of the foot could be regulated at a low level for the purpose of testing the insulating value of various cold weather footgear under conditions approximating those of actual use. Measurements of skin and boot surface temperatures were made simultaneously with determinations of heat loss.

The heat output of the foot was sometimes very low. An example is given in which the heat input into the foot can be calculated to be 21 kg. Cal/M^2/hr. If it is assumed that the blood entered the foot at 36° C. and left at the temperature of the skin the blood flow could have been only about 0.1 ml./min./100 ml. tissue. It is suggested that a mechanism for heat economy exists in precooling the arterial blood. This work was done in close cooperation with Dr. Richard Day of the Climatic Research Laboratory who measured heat loss and blood flow. His work leads to a similar conclusion.

It is pointed out that the rate of cooling is not proportional to insulation if comparisons are made of clothing of varying heat capacities.

BOOK REVIEWS AND NOTICES

MEN, MIND AND POWER. By DAVID ABRAHAMSEN, M.D., Department of Psychiatry, Columbia University. Pp. 195. New York: Columbia University Press, 1945. Price, $2.00.

THIS distinguished author proceeds to "direct attention to the psychologic forces behind the men instrumental in bringing about the most revolting drama the world has ever seen." He asks, and then answers the question, "What kinds of minds do these Nazis who instigated these atrocities have?" The treatise is discussed in the following chapters: The Riddle of the German Spirit; Why Germans Became Nazis; Men on the Scene; Quisling: Abnormal Messiah; Laval: The Man With the Janus Face; Remodelling the Minds of the Germans.

Brief personality sketches are given of the following Germans: Hitler, Goebbels, Goering, Himmler, von Papen, and Hess; also Quisling and Laval. Those Germans are described as maladjusted and as showing additional characteristics: With their insatiable lust for power, their strong emotions, they became engrossed in themselves and acquired a weak personality structure. Individually, they felt insecure and in reality they were rivals. They endeavored to function in the present, but their emotions were living in the past, and that was an old hatred of their immediate surroundings which they transplanted into their broader world.

The author has not meant to relieve Quisling of one iota of responsibility, nevertheless, in considering his disturbed mentality, he says: "He showed signs of mental conflict. Indeed his 'incendiary' speech was so filled with delusions that one gets the impression that he was actually a victim of those delusions for a short while. If we suppose that his condition was somewhat schizophrenic, we can say that Quisling probably barely escaped the disease." . . . "On a basis of his personality make-up, it seems probable that his mental derangement progressed." . . . "—all these make us consider Quisling as an abnormal Messiah." Viewed then, from such an angle, should not the "traitor" have been regarded as only partly responsible? The Germans mentioned, are said to have been criminals before they were "war criminals." Though perhaps showing a bit of emotional bias, the treatise is very interesting and entertaining.

N. Y.

THE CLINICAL APPLICATION OF THE RORSCHACH TEST. By RUTH BOCHNER, M.A., Psychologist, formerly Bellevue Psychiatric Hospital, and FLORENCE HALPREN, M.A., Psychologist, Bellevue Psychiatric Hospital, New York. Pp. 331. Second ed. New York: Grune & Stratton, 1945. Price, $4.00.

IN this edition, the chapters on The Neurotic, The Schizophrenic and The Organic, are enlarged. Those on Intelligence, Behavior Problems and The Alcoholic, are added. The bibliography is more than trebled. There are the inclusions of a psychopathic personality study and an index, as was suggested previously by this Reviewer and it is his belief that since so much time is required for the complete Rorschach procedure, the inclusion of group studies—successfully employed elsewhere—would add to the popularity of the book.

N. Y.

VIRUS AS ORGANISM. Evolutionary and Ecological Aspects of Some Human Virus Diseases. By FRANK M. BURNET, M.D., F.R.S., Director, Walter and Eliza Hall Institute of Research in Pathology and Medicine, Melbourne, Australia. Pp. 134. Cambridge, Mass.: Harvard Univ. Press, 1945. Price, $2.00.

DR. BURNET'S excellent monograph was prepared for the Harvard University Edward K. Dunham Lectures for the Promotion of the Medical Sciences. The manner of treatment is well indicated in the title and subtitle. Viruses are treated from the biologic point of view as organisms under the fundamental necessity of survival in the parasitic state, and viral diseases are shown to represent the dynamic interrelationships between host and parasite, whose long term trend is toward mutual tolerance; this, of course, is a point of view very cogently developed earlier by Theobald

Smith in regard to higher parasitic organisms. In lectures such as these Dr. Burnet in his own words was able "to indulge in speculation about origins and change in virus disease beyond what would be admissible in general scientific writing." The speculations are illuminating and valuable because of the author's wide acquaintance with general biology and his very intensive laboratory experience with viral diseases. Herpes, poliomyelitis, psittacosis and related infections, smallpox, alastrim and vaccinia, yellow fever and influenza in each case receive a chapter. The serious student of virus diseases will derive both pleasure and benefit from Dr. Burnet's treatise.

S. M.

MANUAL OF PSYCHOLOGICAL MEDICINE. For Practitioners and Students. By A. F. TREDGOLD, M.D., F.R.C.P., F.R.S.E., Consulting Physician in University College Hospital, London. Pp. 308; 2 tables. Second ed. Baltimore: Williams & Wilkins, 1945. Price, $5.00.

PSYCHOLOGIC medicine is described as "that branch of medicine which is concerned with disease of mind apart from body." In less than 9 months, the first edition of this work was out of print. In the classification of Mental Disorders, Decay and Defect, the list given is long. The subject matter is discussed in 27 chapters, and in this review some of the more important ones are grouped for space economy: The Normal Mind; General Symptomatology, Anxiety States, Neurasthenia and Epilepsy; the Manic-Depressive, Schizophrenic, Paraphrenia and Paranoia Psychoses; Mental Disorders Due to Toxins, Infections, Syphilis of the Brain, Head Injury, and Those Associated With Child-Bearing, Mental Defect and Moral Defect.

The chief additional matter given is: "Pitressin in the diagnosis of epilepsy; cerebral malaria; mental disorder due to vitamin deficiency; mental disorder due to Parkinsonism; prefrontal leukotomy; alterations in the law in regard to divorce in insanity and infanticide."

Since most subjects with the much discussed psychopathic personality do not become interned in mental hospitals or jails, and since the general practitioner must come in contact with them fairly often, some comprehensive consideration of these disturbers would prove helpful. The great economic and other advantages of foster homes for selected mental and defective subjects is worthy of inclusion. Under Legal Relationships, the descriptions of the care and control of mental disorders and defects, civil relationships and criminal responsibility are those employed in England, and necessarily not wholly applicable here. Otherwise the subject matter is well adapted to the needs of our general practitioners and students.

N. Y.

BACK TO LIFE. The Emotional Adjustment of Our Veterans. By HERBERT I. KUPPER, M.D., Staff Psychiatrist, U. S. Marine Hospital, Ellis Island, N. Y. With a Foreword by DR. ROBERT H. FELIX, Chief, Mental Hygiene Division, U. S. Public Health Service. Pp. 220. New York: L. B. Fischer, 1945. Price, $2.50.

THIS military psychiatrist is well qualified to discuss the perplexing problems of readjusting the fighting wartime emotions of the veterans to peacetime needs, also of readjusting the community. The returning service man is spoken of as less adequate and less secure than before his induction. "He will certainly describe the world around him as less friendly, ungrateful, and vicious . . ." The subject matter is presented in the following chapters: Every Man Is Supposed to Have His Place in the World—But Where Is Mine?; The Fighting Man; Home Again; Native Land; Back to Life. Brief case histories show some of the difficulties and give appropriate measures for overcoming them. Unexpected manifestations may appear: While some artists and writers show impaired ability, others may have greater skill. Following sexual deprivation, for a time there may be psychic impotence; or the veteran may become promiscuous, but little homosexuality is experienced unless the vice was practiced before induction. Instead of quiet following sedation, a sudden release of pent-up memories may result in violence.

The rules of the National Committee of Mental Hygiene are included, some of which are: Love him and welcome him. Listen well. Face the reality of the disability; don't try to ignore it, but don't magnify it. focus on what is left, not what is lost.

Treat him as an essentially normal, upstanding, competent person, not as an invalid. Commend his efforts and successes and ignore the slips. Expect him to be different in some ways. Take time to get acquainted again and to find ways of getting along together. Allow him time and freedom in getting acquainted with the old places and in reëstablishing his old contacts. Create an atmosphere of expectancy: encourage him to take up his favorite hobby or sport, to return to work as soon as he is able, and to lead a normal social life; but avoid pushing or regulating him. Get professional help if it is needed. Don't just muddle through. Let your own faith and beauty of spirit be your chief stock-in-trade. N. Y.

NEW BOOKS

Human Embryology (Prenatal Development of Form and Function). By W. J. Hamilton, M.D., D.Sc., F.R.S.E., Professor of Anatomy in the University of London at the Medical College of St. Bartholomew's Hospital; and J. D. Boyd, M.A., M.Sc., M.D., former Fellow of Clare College, Cambridge; Professor of Anatomy in the University of London at the Medical College of the London Hospital. Pp. 366. Baltimore: Williams & Wilkins, 1945. Price, $7.00.

Back to Life. The Emotional Adjustment of Our Veterans. By Herbert I. Kupper, M.D., Staff Psychiatrist, U. S. Marine Hospital, Ellis Island, N. Y. With a Foreword by Dr. Robert H. Felix, Chief, Mental Hygiene Division, U. S. Public Health Service. Pp. 220. New York: Fischer, 1945. Price, $2.50.

Physical Chemistry of Cells and Tissues. By Rudolf Hober, University of Pennsylvania School of Medicine, Philadelphia. Pp. 676; 70 ills. Phila.: Blakiston, 1945. Price, $9.00.

Cleft Palate and Speech. By Muriel E. Morley, B.Sc., F.C.S.T., Speech Therapist to the Royal Victoria Infirmary, The Hospital for Sick Children, and The Newcastle General Hospital, Newcastle-upon-Tyne. Pp. 156. Baltimore: Williams & Wilkins, 1945. Price, $2.75.

The Medical Clinics of North America. Symposium on Gynecology and Obstetrics. Philadelphia Number. Phila.: Saunders, 1945. Price, $16 per year.

Vitamins and Hormones. Vol. III. Edited by Robert S. Harris, Assoc. Professor of Nutritional Biochemistry, Massachusetts Institute of Technology, Cambridge, Mass., and Kenneth Y. Thimann, Assoc. Professor of Plant Physiology, Harvard University, Cambridge, Mass. Pp. 420; numerous figs. and tables. New York: Academic Press, 1945.

Hematology. For Students and Practitioners. By Willis M. Fowler, A.B., M.D., Professor of Internal Medicine, University of Iowa, Iowa City. With a Chapter by Elmer L. Degowin, A.B., M.D., Assistant Professor of Internal Medicine, University of Iowa. Pp. 499; 110 figs. New York: Hoeber, 1945. Price, $8.00.

The Bacterial Cell. In Its Relation to Problems of Virulence, Immunity and Chemotherapy. By Rene J. Dubos, George Fabyan Professor of Comparative Pathology and Professor of Tropical Medicine, Schools of Medicine and Public Health, Harvard University, Member of the Rockefeller Institute. With an Addendum by C. F. Robinow, Strangeways Laboratory, Cambridge, England. Pp. 460. Cambridge, Mass.: Harvard Univ. Press, 1945. Price, $5.00.

The Extremities. By Daniel P. Quiring, Ph.D., Head of the Anatomy Division, Cleveland Clinic Foundation, and Assoc. Professor of Biology, Western Reserve University. Pp. 117; 106 engravings. Phila.: Lea & Febiger, 1945. Price, $2.75.

Dr. W. C. Röntgen. By Otto Glasser, Cleveland Clinic Foundation. Pp. 169. Springfield, Ill. Charles C Thomas, 1945. Price, $4.50.

NEW EDITIONS

The Clinical Application of the Rorschach Test. By Ruth Bochner, M.A., Psychologist formerly Bellevue Psychiatric Hospital, and Florence Halpern, M.A., Psychologist, Bellevue Psychiatric Hospital, New York. Second ed. Pp. 331. New York: Grune & Stratton, 1945. Price, $4.00.

Prescribing Occupational Therapy. By William Rush Dunton, Jr., M.D. Second ed. Pp. 151. Springfield, Ill.: Thomas, 1945. Price, $2.50.

Modern Urology for Nurses. By SHEILA MAUREEN DWYER, R.N., B.S., Director, School of Nursing and Nursing Service, Southampton Hospital, Southampton, N. Y., and GEORGE W. FISH, M.D., Associate Professor of Urology, College of Physicians and Surgeons, Columbia University, New York City. Second ed. Pp. 287; 66 engr. Phila.: Lea & Febiger, 1945. Price, $3.25.

The Physician's Business. Practical and Economic Aspects of Medicine. By GEORGE D. WOLF, M.D., Assistant Clinical Professor of Otolaryngology, New York Medical College, New York; Fellow, New York Academy of Medicine. Foreword by HAROLD RYPINS, A.B., M.D., F.A.C.P. Second ed. Pp. 433; 58 ills. Phila.: Lippincott, 1945. Price, $6.00.

This book aims to show how to "systematize work to be done, and how to institute many tested time and money-saving ideas.

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